ALICYCLIC DIKETONES and DIOLS.

A Thesis

submitted to Glasgow University

for the degree of Doctor of Philosophy

by

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Summary of Thesis.

SUMMARY

cis- and trans-2:2:5:5-Tetramethylcyclohexane-1:3-diol were prepared from 5:5-dimethylcyclohexane-1:3-dione (dimedone) and, contrary to previous findings, the low-melting diol was shown to be the trans-isomer by resolution through the bis-(-)-menthoxyacetates. The cis-diol was shown, by infrared methods, to have the diequatorial conformation.

Dehydration of both cis- and trans-2:2:5:5-tetramethylcyclohexane-1:3-diol with potassium bisulphate gave 1:1-dimethyl-4-isopropylidenecyclopent-2-ene, 2:3:5:5-tetramethylcyclohexanone and 2:2:5:5-tetramethylcyclohex-3-enol. The diene was hydrogenated to 1:1-dimethyl-3-isopropylcyclopentane which was synthesised from (+)-fenchone. 2:3:5:5-Tetramethylcyclohex-2-enone and 2:2:5:5-tetramethylcyclohexanol were both synthesised from dimedone and correlated with the saturated ketone and unsaturated alcohol respectively from the dehydrations of the diols. Mechanisms were put forward for the dehydrations.

In an attempt to synthesise α-pinene, 4-methoxycarbonyl-5:5-dimethylcyclohexane-1:3-dione (Vorlander's ester) was prepared and the structure of its enol ether elucidated. Lithium aluminium hydride reduction of the enol chloride of Vorlander's ester gave 3-chloro-5:5-dimethyl-6-hydroxymethylcyclohex-2-enol.

Dieckmann cyclisation of 1:6-diethoxycarbonylhexan-2-one, synthesised from ethyl hydrogen adipate, gave not the anticipated cycloheptane-1:3-dione, but 2-(carboethoxyacetyl)-cyclopentanone and a further cyclisation product, 4-hydroxy-5:6-trimethylene-2-pyrone. The former was converted to 2-(carbobenzyloxyacetyl)-cyclopentanone and hence to 2-acetyl-cyclopentanone which was also obtained by hydrolysis of the pyrone. The ultra-violet spectra of several acylcyclanones, β-keto-esters and their copper enolates were studied.

CONTENTS

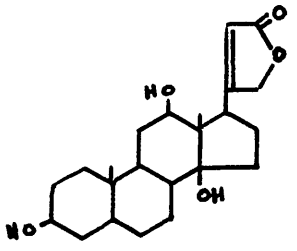
CONTENTS (contd.)

PART I

INTRODUCTION

Although dehydrations of a variety of aliphatic 1:3-diols have been thoroughly examined, a similar study of the corresponding alicyclic compounds has been virtually overlooked.

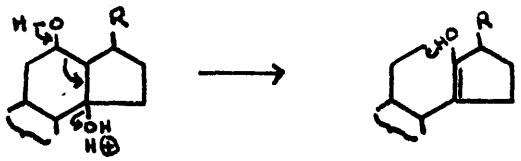
Dehydration of a 1:3-diol system of known stereochemistry appeared to be particularly attractive since such a system is present in several of the heart poisons (e.g. digoxigenin (1)).



(1)

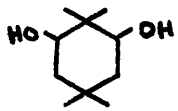
It might be expected that a compound such as (1), by analogy with open chain compounds[1,2] would undergo ring cleavage on treatment with potassium bisulphate to give the open chain aldehyde (2) and this would then be diagnostic of the presence of a 1:3-diol system*.

* Since aglycones are unstable to alkali this reaction has an advantage over the base catalysed rearrangement of p-toluenesulphonates.



(a)

However, due to the inaccessibility of the appropriate heart poison or aglycone it was decided to investigate dehydrations of the model substance 2:2:5:5-tetramethyl-cyclohexane-1:3-diol (3), which, like digoxigenin is fully substituted on the carbon atom between the two hydroxyl groups.

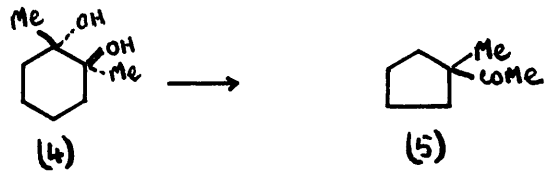


(3)

From this study would emerge the relationship between the stereochemistry of a cyclic 1:3-diol and its mode of dehydration.

Bartlett and his coworkers have already endeavoured to elucidate this relationship for cyclic 1:2-diols. It had been shown that trans-1:2-dimethylcyclohexane-1:2-diol (4) was dehydrated with mineral acid to give 1-acetylmethyl-cyclopentane[3] (5) and Bartlett and Pockel reported[4] that the cis-isomer (6) reacted under similar conditions to

give 2:2-dimethylcyclohexanone (7).

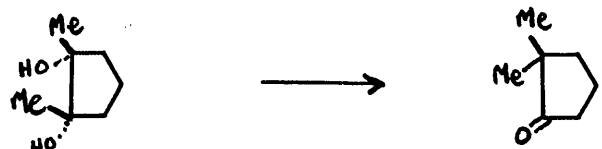


(4) (5)

(6) (7)

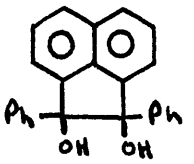
However when the latter reaction was reinvestigated by Meerwein some time later[5] it was shown that 1-acetyl-methylcyclopentane was actually the dehydration product; the ketone was isolated as its semicarbazone and its structure proven by oxidation to 1-methylcyclopentane-carboxylic acid. That a mixture might result from this dehydration seems very probable (see page 41), the lesser components having been overlooked in the isolation procedure.

Dehydration of cis-1:2-dimethylcyclopentane-1:2-diol (8) yielded 2:2-dimethylcyclopentanone (9), (isolated as the crude semicarbazone) while the trans-diol gave only tars probably arising from polymerisation of a diene formed in the reaction[6].



(8) (9)

Both cis- and trans-7:8-diphenylacenaphthene-7:8-diol (10), on acidic dehydration[7] yielded 8:8-diphenylacenaphthene-7-one (11) but under the reaction conditions the trans form isomerised to the cis.



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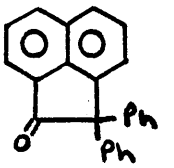
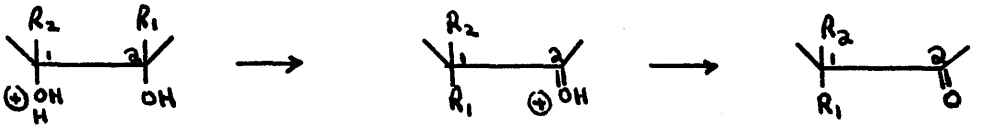


(11)

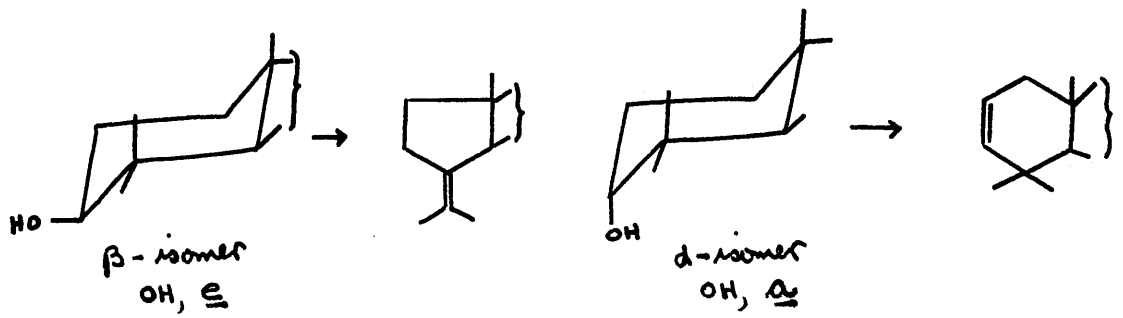
On the basis of these reactions Bartlett postulated a mechanism for the dehydrations involving protonation of one of the hydroxyl groups followed by removal of water and migration of the neighbouring group.



He concluded that the migrating group was by preference the one which is "located in space near the opposite side of carbon atom number 1 to that occupied by the hydroxyl group which is to be replaced."

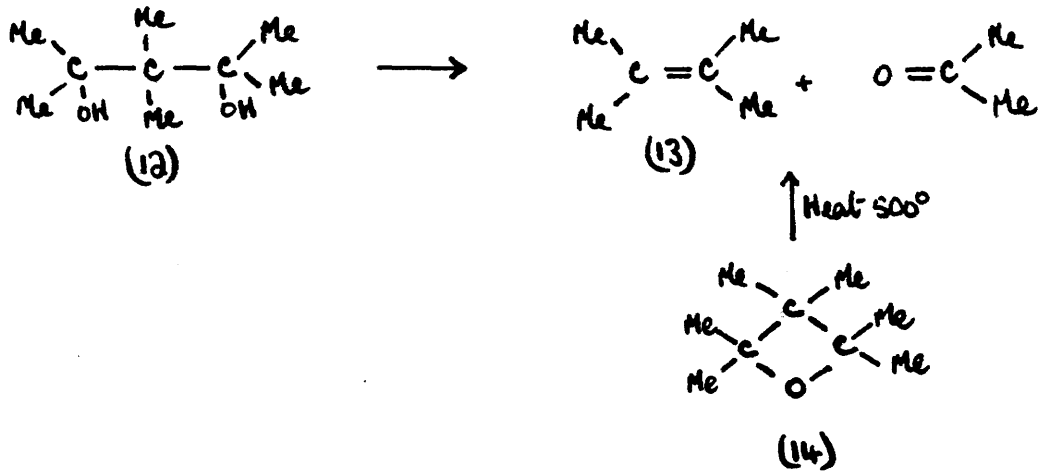
Some years later, after the mechanism of bimolecular eliminations had been established and the concepts of concerted mechanisms and conformations of molecules

accepted, Hughes, Ingold[8] and Barton[9] suggested that in E_2 reactions and migrations the substituent and pair of electrons involved are trans antiparallel to the group being eliminated. The formation of different products from the isomeric α- and β-lanosterols is readily explained thus:-

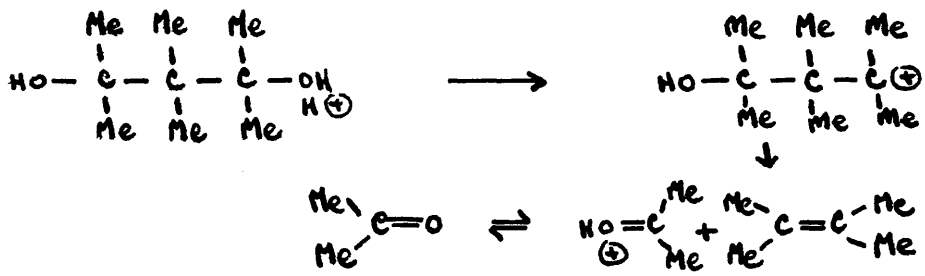


The mechanism of dehydration of aliphatic 1:3-diols has been thoroughly investigated although studies of conformationally rigid systems have been very limited.

Hexamethylpropane-1:3-diol (12) when treated with acidic reagents yielded tetramethylethylene (13) and acetone[10], and these same products were obtained on thermal degradation of the oxide (14)[11].

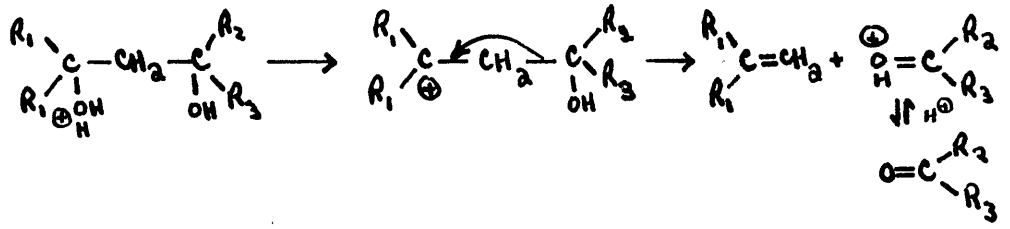


Also, certain 1:3-diols with dilute mineral acids yielded small quantities of oxides, and on the basis of all of these reactions Barbot postulated that an oxide was an intermediate in the dehydration of these diols. However Whitmore suggested[12] that the mechanism of the dehydration of hexamethylpropane-1:3-diol was essentially ionic.



Some years later, English and his collaborators studied the dehydration, with potassium bisulphate, of a variety of aliphatic 1:3-diols and in all such cases investigated a cleavage of the molecules into

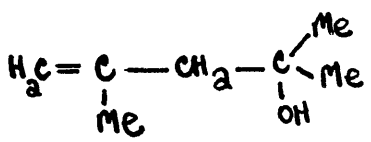
carbonyl compounds and olefins was observed[2]. The mechanism proposed for the reaction was essentially the same as that suggested by Whitmore for the cleavage of hexamethylpropane-1:3-diol.



Where R_1 = Ph and R_2 = R_3 = C_2H_5 the products and yields were:-

$Ph_2C = CH_2$, 56%; $(C_2H_5)_2C = O$, 66%; $Ph_2C = O$, 1%.

An alternative mechanism was considered involving normal 1:2-elimination of a molecule of water to give an unsaturated alcohol which would then cleave by protonation of the double bond. However 2:4-dimethylpent-4-en-2-ol (15) yielded no acetone under conditions which gave acetone (15% yield) from the diol (16).



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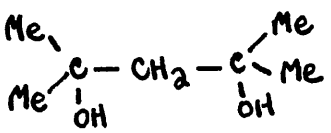
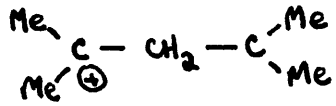
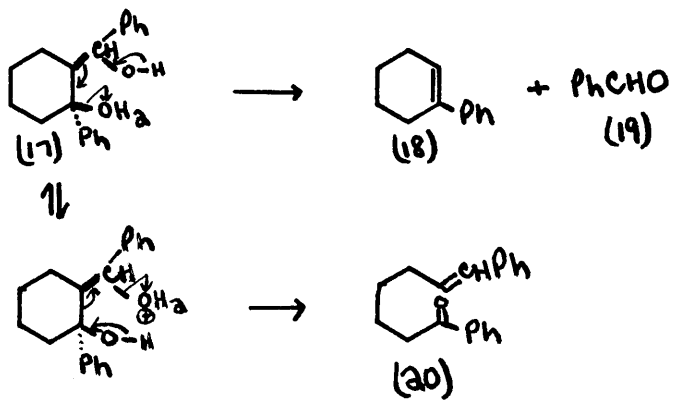


(16)

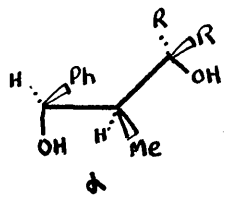
But since the olefin (15) was cleaved by concentrated sulphuric acid to give acetone (in 31% yield) Brutcher suggested that although this olefin is not a necessary intermediate in the cleavage of the diol (16) both compounds undergo fission through the common carbonium ion:-



Zimmerman and English went on to study[13] the effect of stereochemistry and substitution on the dehydration of 1:3-diols. 1-Phenyl-2-(α-hydroxybenzyl)-cyclohexanol [tentatively assigned configuration (17)] with potassium bisulphate or dilute sulphuric acid yielded phenyl-cyclohexene (18) and benzaldehyde (19) or 1:7-diphenyl-hept-1-en-7-one (20) depending on which hydroxyl group was originally protonated.

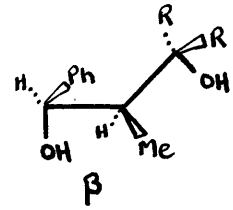


Diastereoisomeric α- and β-1-phenyl-2-methyl-3-ethylpentane-1:3-diol [(21); R = C_2H_5] and -1:1:3-triphenyl-2-methylpropane-1:3-diol [(21); R = Ph] were synthesised and their configurations proven by relation to dl-nor-ψ-ephedrine (22).

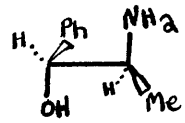


α

(21)



β



(22)

Both isomers were treated with ethanolic sulphuric acid and benzaldehyde isolated as its 2:4-dinitrophenylhydrazone. It was found that when R is ethyl the β-isomer cleaved faster than the α-isomer and vice versa when R is phenyl.

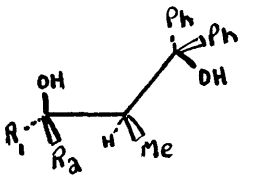
A study of the acidic cleavage reaction of the diastereoisomeric 2-phenyl-3-methyl-4-ethylhexane-2:4-diols (23), (arbitrarily designated α and β) showed that, of the two, the β-isomer cleaved more readily (see Table 1). Only the carbonyl compounds in the reaction products were characterised.

(23)

Table 1

Products	α-isomer	β-isomer
EtCOEt	5%	75%
PhCOMe	35%	-

On the basis of these reactions a mechanism was put forward for the dehydrations involving a 4-membered cyclic transition state. α-1:1:3-Triphenyl-2-methyl-propane-1:3-diol [(21); R_1 = Ph, R_2 = H] of proven configuration would give a transition state (21t), in which the phenyl (R_1) and methyl groups on adjacent carbon atoms are located on different sides of the molecule, whereas in the β-isomer [(21); R_1 = H, R_2 = Ph] these groups would be on the same side. Hence the α-isomer giving the transition state of lower energy would cleave more readily.



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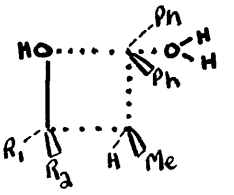


(21t)

In order to explain the formation of two carbonyl compounds from the cleavage of the isomeric 2-phenyl-3-methyl-4-ethylhexane-2:4-diols two transition states involving proton attack at either hydroxyl group were postulated. The differences in reactivity of the two isomers were then based on the different steric requirements of the phenyl and methyl groups in the transition states.

The oxide ring hypothesis outlined above has several defects:-

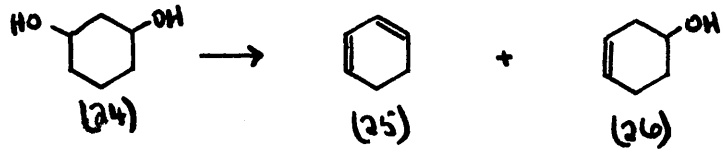
(1) Since mobile systems were used, the conformations of the molecules and hence, a postulated mechanism for the reaction were highly speculative.

(2) Cleavage of the α- and β-isomers of 1-phenyl-2-methyl-3-ethylpentane-1:3-diol was contrary to predictions based on the hypothesis.

(3) In no experiment was the olefinic product characterised.

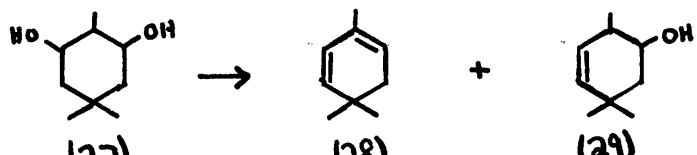
It has already been mentioned that very little work has been done on the dehydration of cyclic 1:3-diols.

Cyclohexane-1:3-diol (24), when distilled with iodine yielded 1:3-cyclohexadiene (25) and cyclohex-3-enol (26)[14].



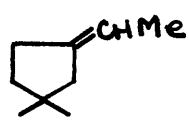
(24) (25) (26)

2:5:5-Trimethylcyclohexane-1:3-diol (27) of uncertain configuration, on dehydration with potassium bisulphate yielded a diene C_9H_{14} and an alcohol $C_9H_{16}O$ formulated as (28) and (29) respectively[15].



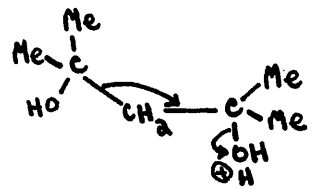
(27) (28) (29)

Oxidation of the diene with potassium permanganate followed by treatment of the resulting lactonic acid with silver nitrate gave 2:2-dimethylsuccinic acid. On the basis of these reactions the structure of the diene could equally well be (30), a fact which had been overlooked by Hirsjarvi.



(30)

In the studies of English and Brutcher on the dehydration of aliphatic 1:3-diols[2], a concerted trans-elimination was considered involving removal of the hydroxyl group and simultaneous migration of the requisite antiparallel pair of electrons [see (16)].



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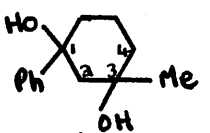

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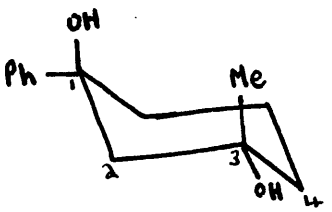


(31c)

It was anticipated that if this were the case, steric factors would affect the course of the reaction. Therefore a comparison was made of the dehydrations of 2:4-dimethylpentane-2:4-diol (16) and 1-phenyl-3-methylcyclohexane-1:3-diol (31). While the former gave a yield of 15% of acetone on dehydration with potassium bisulphate the latter gave no detectable yield of carbonyl compound, but only an unsaturated oil (λ_{max} 249-250 mμ).

It was assumed that the conformation of the molecule was (31c) and that normal 1:2-elimination of water had taken place between C_1 and C_2 presumably giving rise ultimately to a homoannular diene. However the mode of dehydration of the diol seemed to be conjecture, since:-

(a) No evidence had been put forward concerning the configuration of the substituents (Ph, Me and -OH's) although the conformation (31c) had been assumed.

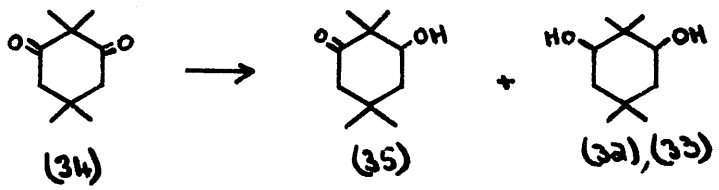
(b) The olefinic product was not characterised.

Thus, in view of the scanty information available concerning the dehydration of the cyclic diol it would be unfair to attempt to compare this reaction with the dehydration of the open chain diol.

It was apparent from these considerations that the dehydration of a cyclic 1:3-diol of known configuration had yet to be undertaken, the products characterised, and the mechanism of the reaction clarified. Also, if a cleavage of the molecule into an open chain aldehyde did take place the reaction could be applied in the field of the heart poisons. From both of these aspects cis- and trans-2:2:5:5-tetramethylcyclohexane-1:3-diol (32), (33) appeared to be the most suitable, readily accessible

model compounds for dehydration studies.

Hirsjarvi had prepared these stereoisomers[16] by the electrolytic reduction of dimethyldimedone (34) to 3-hydroxy-2:2:5:5-tetramethylcyclohexan-1-one (35) and reduction of the latter with sodium amalgam.



(34) (35) (32), (33)

The high and low melting diols (subsequently referred to as diols A and B respectively) were claimed to have the trans and cis configurations respectively mainly on the basis of their physical properties; attempts by Hirsjarvi to resolve diol A were unsuccessful.

Thus before embarking on dehydration experiments it was first necessary to have more concrete evidence about the configurations of these diols.

DISCUSSION

(a) cis- and trans-2:2:5:5-Tetramethylcyclohexane-1:3-diol.

The methylation of dimedone is reported as giving[17,18] a maximum yield of 25% of dimethyldimedone. Attempts to improve this yield by varying the molecular proportions of methyl iodide and sodium methoxide and also by using potassium tert-butoxide in benzene were unsuccessful. The methylation was finally carried out in two stages; the first yielded a mixture of di- and monomethyldimedone and the latter which was alkali soluble was remethylated.

2:2:5:5-Tetramethylcyclohexane-1:3-dione was smoothly reduced with lithium aluminium hydride to a mixture of cis- and trans-2:2:5:5-tetramethylcyclohexane-1:3-diol. Substantially pure diol A (m.p. 204.5°) was obtained by an initial crystallization from ether. Benzoylation of the residue and chromatography of the crude dibenzoate yielded pure diol B dibenzoate which on hydrolysis gave pure diol B (m.p. 110-112°).

When working on a large scale, it was possible to separate the diols by fractional crystallization.

The method used by Rigby[19] for the resolution of trans-cyclohexane-1:3-diol was applied to the above diols.

The dimonoacidphthalate of each diol was prepared, but treatment of either with brucine, quinine or (+)-(α)-phenylethylamine in methanol solution failed to give a crystalline salt.

Read and Wilson have resolved trans-cyclohexane-1:2-diol via its mono-(-)-menthoxyacetate[20]. However, since difficulties had been encountered in the preparation of the monobenzoates of diols A and B* it was decided to attempt a resolution of the bis-(-)-menthoxyacetates.

Diol A bis-(-)-menthoxyacetate was a crystalline solid whose specific rotation, $[\alpha]_D^{19}$ -71.69°, was unchanged on repeated crystallization. Alkaline hydrolysis of the diester gave diol A with zero rotation.

Diol B gave an oily bis-(-)-menthoxyacetate which was purified by distillation. In a preliminary experiment it was established that a partial separation of the diastereoisomers could be effected by chromatography of the diester on alumina, the specific rotations of the first and last fractions differing by 20°. The experiment was then repeated on a preparative scale. Hexane and ether eluted diesters having $[\alpha]_D^{20}$ -66.4° and $[\alpha]_D^{20}$ -59.0° respectively. These fractions were then rechromatographed and the pure diastereoisomeric bis-(-)-menthoxyacetates

* Instead of the monobenzoate of the diol an unsaturated ester with no hydroxyl group, was obtained.

obtained as waxy solids each with m.p. 59° and having $[\alpha]_D^{21}$ -75.6° and $[\alpha]_D^{21}$-54.5° respectively.

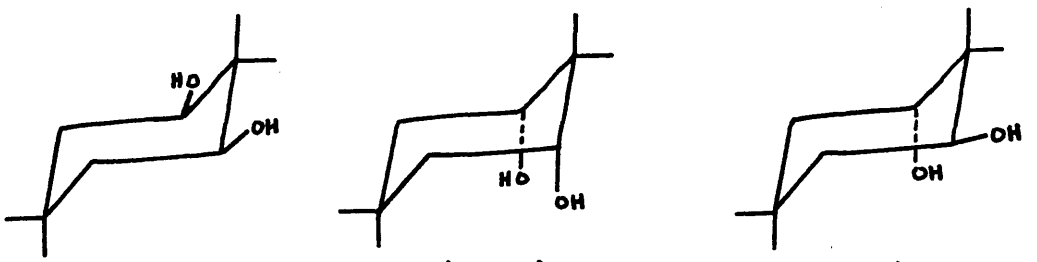
Hydrolysis of the diastereoisomer, $[\alpha]_D^{21}$-75.6°, yielded (-)-trans-2:2:5:5-tetramethylcyclohexane-1:3-diol, $[\alpha]_D^{23}$ -19.4°, m.p. 134-137° (m.p. racemate 110-112°) and hydrolysis of the second diastereoisomer, $[\alpha]_D^{21}$ -54.5°, yielded (+)-trans-2:2:5:5-tetramethylcyclohexane-1:3-diol, $[\alpha]_D^{23}$ +22.8°, m.p. 125-126°.

The resolution of diol B into d and l forms shows that the compound has no plane of symmetry and thus contrary to the findings of Hirsjarvi has the trans configuration; it follows therefore that diol A is the cis-isomer.

(b) <u>The conformations of certain cyclohexanols and cyclohexane-1:3-diols</u>.

During a study of the conformation of cis-2:2:5:5-tetramethylcyclohexane-1:3-diol (diol A) the infrared spectra of this and of a number of related compounds were determined.

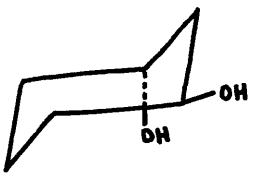
There are two possible chair conformations of cis-2:2:5:5-tetramethylcyclohexane-1:3-diol ($32c_1$) and ($32c_2$) and only one of the trans isomer (33), it was hoped to elucidate the conformation of the former by infrared methods.



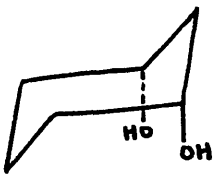
($32c_1$) ($32c_2$) (33)

Kuhn has studied the infrared spectra of cis- and trans-cyclohexane-1:2- and-1:3-diols[21] and has shown that in these compounds in which intramolecular hydrogen bonding occurs two bands appear in the region of the -OH stretching vibration at about 3620 cm.$^{-1}$ and 3540 cm.$^{-1}$ [22]. The infrared spectrum of trans-cyclohexane-1:3-diol (36) showed only one band (ν_{max} 3620 cm.$^{-1}$) while that of the

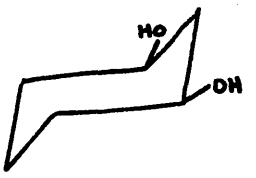
cis compounds ($37c_1$) or ($37c_2$) showed two (ν_{max} 3619, 3544 cm.$^{-1}$) indicating that the latter exists in the diaxial conformation ($37c_1$) since only then is intramolecular hydrogen bonding possible.



(36)



($34c_1$)

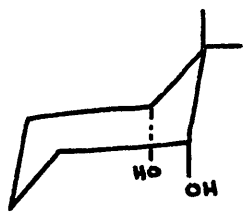


($34c_2$)

In the present case, since the infrared spectra of both diols A and B showed only one hydroxyl stretching band (Table 3, page 25) it was concluded that the cis-isomer was not intramolecularly hydrogen bonded and must therefore exist in the diequatorial conformation ($32c_1$).

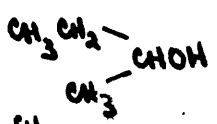
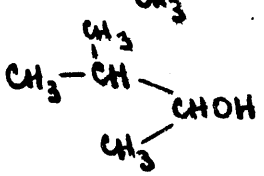
The different conformational preference of cis-2:2:5:5-tetramethylcyclohexane-1:3-diol as compared with cis-cyclohexane-1:3-diol appears to be due to the "1:3-steric interaction" between the methyl and hydroxyl groups in the diaxial form of the former compound. Hence, the increased stability of the diaxial form, gained through hydrogen bonding is counteracted by this 1:3-interaction and the molecule adopts the more stable diequatorial conformation. In 2:2-dimethylcyclohexane-1:3-diol there is no 1:3-interaction between methyl and

hydroxyl and it would follow therefore that the cis isomer should adopt the diaxial conformation (38). It was found that this diol[23] (only one isomer was isolated) did in fact exhibit two peaks in the -OH stretching region (Table 3) indicating the presence of intramolecular hydrogen bonding* and showing that the hydroxyl groups were in fact cis and diaxial.



(38)

The effect of substitution on the C-O stretching frequency in cyclohexanols is seen by comparing the spectra of differently substituted compounds. It has been found that in aliphatic secondary alcohols substitution at the α-carbon atom has generally the effect of displacing the C-O absorption band to lower frequencies[24].

	C-O Stretching Band cm^{-1}
	1105
	1090

* The solution concentration (.001M) was such that intramolecular hydrogen bonding was impossible.

α-Substitution in cyclohexanols of similar conformation appears to have the opposite effect (Table 2), i.e. the C-O stretching vibration is displaced to higher frequencies with increased substitution.

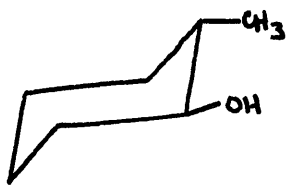
Table 2

Compound	C-O stretching vibration cm.$^{-1}$	
Cyclohexanol	1030 m	
Trans-1-methylcyclohexanol	1040 s	
Cis-cyclohexane-1:3-diol[56]	1016 s	1033 s
Cis-2:2-dimethylcyclohexane-1:3-diol	1018 s	1046 s
Trans-cyclohexane-1:3-diol[56]	978 s	1027 m
Trans-2:2:5:5-tetramethylcyclohexane-1:3-diol	1003 s	1047 s

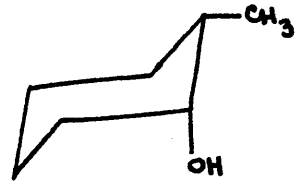
The effect of conformation on the C-O stretching frequency in cyclohexanols has been studied by a number of workers. Bands near 1060 cm.$^{-1}$ and 1040 cm.$^{-1}$ have been variably assigned to equatorial nydroxyl groups and near 1000 cm.$^{-1}$ and 955 cm.$^{-1}$ to axial hydroxyl groups[25,26]. It may be said that, generally for an

equatorial hydroxyl group the C-O stretching frequency is higher than for the corresponding axial group.

The infrared spectrum of trans-2-methylcyclohexanol[27] (Table 3) showed medium and strong bands at 1066 and 1040 cm.$^{-1}$ respectively confirming the expected diequatorial conformation (39).



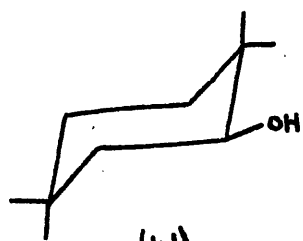
(39)



(40)

The strong band at 975 cm.$^{-1}$ in the spectrum of the cis-isomer (40)[27] suggests that the hydroxyl group is axial and the bulky methyl group equatorial as would be expected.*

The strong C-O stretching frequency of 2:2:5:5-tetramethylcyclohexanol (41), (see page 25) at 1036 cm.$^{-1}$ suggests that in this compound the hydroxyl group is purely equatorial.



(41)

* Cole et al.[28] have recently come to the same conclusions from a study of the -OH stretching region.

The complexity of the spectra of the diols however in the C-O region (Table 3) defeats any simple attempt to correlate band frequencies with conformation.

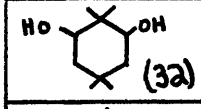
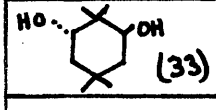
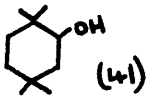
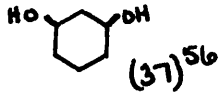
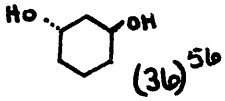
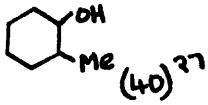
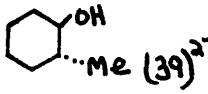
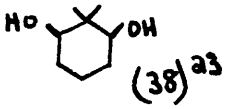
The relationship between the conformations of cyclohexanols and their -OH stretching frequencies has recently been studied (cf.[28]). For compounds in which the hydroxyl group is axial the -OH band appeared at higher frequencies than for the corresponding equatorially substituted compounds.

This relationship is clearly seen in the compounds in Table 3. Diol B (-OH's a,e) shows a higher -OH stretching frequency than diol A (-OH's e,e) which in turn is comparable with 2:2:5:5-tetramethylcyclohexanol (-OH, e). The conformations of cis- and trans-2-methylcyclohexanols (also studied by Cole et al.[28]) can similarly be correlated with their -OH stretching frequencies.

It is seen from a survey of the literature that infrared methods in certain favourable cases are of use in determining conformation. However, it is apparent that the applicability of the technique in the C-O region of the spectrum is quite limited and as yet no general conclusions relating the conformations of cyclohexanols with the C-O stretching frequencies have been made.

Table 3

The Infrared Spectra of Cyclohexanols and cyclohexane-1:3-diols*.

Compound	-OH Stretching Vibration ($cm.^{-1}$)	Region of C-O Stretching Vibration ($cm.^{-1}$)
β-Cholestanol	3623 (CCl_4) 3608	1080 m, 1043 s, 957 w.
 (32)	3617	1088 m, 1023 s, 997 s.
 (33)	3623	1047 s, 1003 s.
 (41)	3617	1077 w, 1036 s, 1012m, 982 w, 963 w.
 (37)[56]	3609) 3540)	1065 m, 1033 s, 1016 s, 962 w, 947 m.
 (36)[56]	3612	1064 s, 1027 m, 978 s.
 (40)[27]	3622	1074 w, 1015 w, 990 w, 975 s, 945 w.
 (39)[27]	3617	1094 w, 1066 m, 1040 s, 984 w, 929 w.
 (38)[23]	3617) 3537)	1092 m, 1046 m, 1018 s, 980 m, 952 m.

* Determined with a Unicam, SP. 100, Infrared Spectrometer, using a sodium chloride prism and SP. 130 grating accessory. All spectra are in CS_2 solution unless otherwise indicated.

(c) The dehydration of cis- and trans-2:2:5:5-tetramethyl-cyclohexane-1:3-diol

With the configuration of diols A and B now firmly established the way was open for a study of their dehydration products.

The diol was heated with potassium bisulphate at 160-180° in vacuo and the products (oil and water) collected in an acetone-carbon dioxide trap. The cis- and trans-diols gave 2.0 and 1.2 mols. of water respectively (considering the total weight of product to be equivalent to the total weight of diol which had reacted) which suggested that the oily product from the trans-diol still contained a considerable percentage of oxygen.

In each case the infrared spectrum suggested that the oil consisted of a mixture of unsaturated hydrocarbon, carbonyl compound and alcohol and as expected, the proportion of alcohol and ketone from the trans-diol appeared to be very much greater than from the cis-diol (cf. Table 4).

Table 4

Infrared frequencies cm^{-1}				
	oil_c	3240 w	1705 m	880 m 816 m, 768 s.
	oil_t	3240 s	1705 vs	878 m, 816 w, 763 s.
Assignment		-OH	C=O	Unsaturation.

Oil_c = oil from cis-diol.

Oil_t = oil from trans-diol.

All attempts to separate the reaction products from either diol by derivative formation were unsuccessful. The ketone could be removed as its 2:4-dinitrophenylhydrazone but the unsaturated material appeared to undergo decomposition under the acidic conditions of the experiment. Chromatography of the reaction product on alumina proved to be successful and in this way, using isopentane as the initial eluant, the mixture from either diol was separated into unsaturated hydrocarbon, ketone and alcohol. The products (the percentages by weight are given in Table 5) from the cis- and trans-diols were shown to be identical by a comparison of their infrared spectra and retention times on vapour phase chromatography.

Table 5

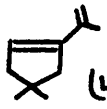
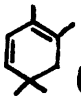
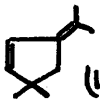
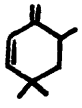
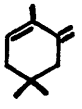
	Trans-Diol	Cis-Diol
Unsat. hydrocarbon	53	88
Ketone	30	12
Alcohol	17	

The unsaturated hydrocarbon $C_{10}H_{16}$ isolated from the isopentane eluate underwent rapid oxidation in air (as was seen from the hydroxyl and carbonyl peaks which had developed in its infrared spectrum). The compound did not give a crystalline adduct with maleic anhydride but

the presence of a conjugated diene system in the molecule was shown by its ultra-violet and infrared spectra respectively (see page 57). On catalytic hydrogenation, the diene absorbed 2 mols. of hydrogen giving the saturated hydrocarbon $C_{10}H_{20}$.

The five most probable structures for the diene (42) to (46), and their theoretical ultra-violet absorption maxima are given in Table 6. β-Phellandrene (48)[29] and 1:3-cyclohexadiene (47)[29] are included for comparison purposes.

Table 6

Structure	λ_{max}, mμ	Structure	λ_{max}, mμ.
 (42)	232[30]	 (46)	264[c]
 (43)	242[30]	 (47)	256
 (44)	232[a]	 (48)	232
 (45)	234[b]	Unknown Diene $C_{10}H_{16}$	243

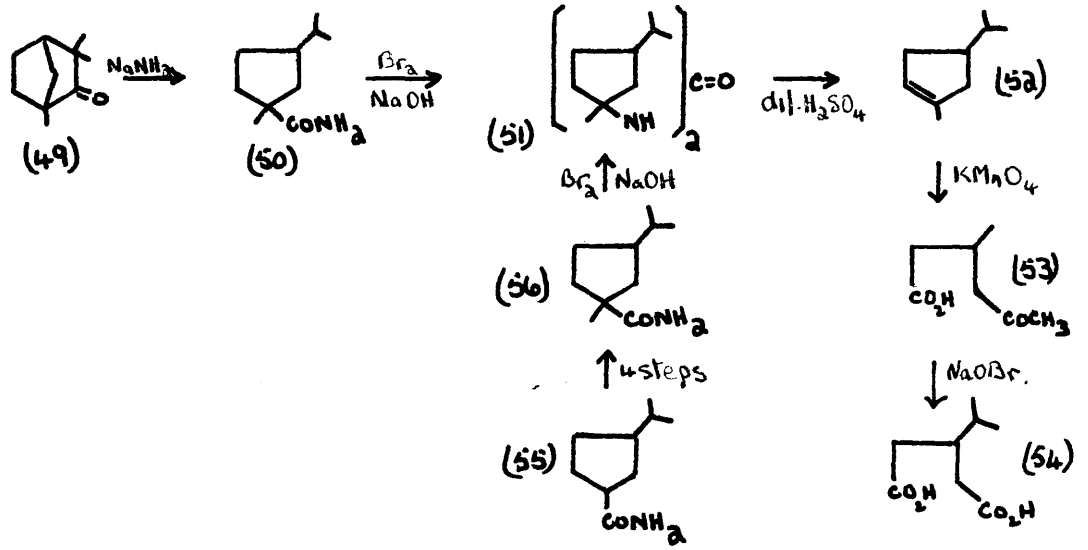
(a) The chromophore is equivalent to that of β-phellandrene.

(b) β-Phellandrene chromophore with one substituent[30].

(c) 1:3-Cyclohexadiene chromophore with two substituents.

From these considerations (Table 6) it appears that none of the structures (42) to (45) could be completely ruled out. However repeated attempts to isolate formaldehyde (as its dimedone derivative) or formic acid (as its sodium salt) from the ozonolysis of the diene were unsuccessful so that any structure involving a methylene group is excluded. Furthermore, the isolation of acetone (as its 2:4-dinitrophenylhydrazone) from these ozonolyses establishes the presence of an isopropylidene group in the molecule. Also, structures (44) and (45) were later excluded by the evidence for the skeletal structure of the diene [cf. synthesis of hydrocarbon (57), page 30].

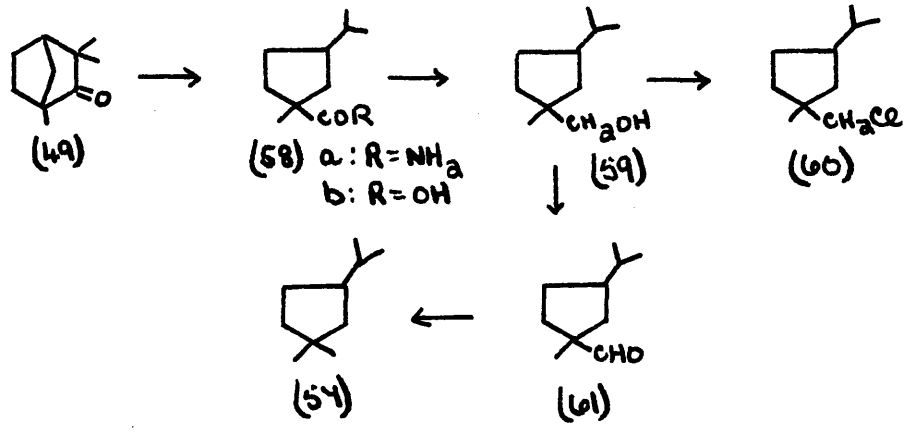
The nature of the diene skeleton was confirmed by a correlation with a prolification product of fencholic acid. The structure of fencholamide (and hence fencholic acid) has been established in the following way:[31, 32, 33.]



Camphenilamide (55) of established structure[34] was converted to a fencholamide (56) evidently stereoisomeric with that obtained from (+)-fenchone since both gave the same difencholylurea (51)[33]. This, together with the degradative evidence confirmed structure (50) for fencholamide.

In the present work 1:1-dimethyl-3-isopropylcyclopentane (57) was wanted for a direct comparison with the saturated hydrocarbon $C_{10}H_{20}$ obtained from the diene $C_{10}H_{18}$.

(+)-Fenchone (49) was converted to (+)-fencholamide (58a) by treatment with sodium in liquid ammonia and the (+)-fencholamide was smoothly hydrolysed to (+)-fencholic acid (58b) by the action of nitrous acid[35]. (The known method for hydrolysing fencholamide was slow and the conditions were drastic. The present improved method was developed by J.M. Wilson)[36].



(+)-Fencholic acid was smoothly reduced with lithium aluminium hydride to (+)-dihydrofenchyl alcohol (59). Two routes were exploited for converting (+)-dihydrofenchyl alcohol into the saturated hydrocarbon (57). In the first method the alcohol (59) was converted into the corresponding chloride (60)[37]. However, the product isolated gave a positive tetranitromethane test and the analytical data suggested that a considerable quantity of impurity was present. Reduction of the crude chloride with zinc dust in acetic acid[37] gave a hydrocarbon which contained substantial quantities of unsaturated material, (from its infrared spectrum and positive tetranitromethane test).

The alternative method of oxidation of the alcohol to the corresponding aldehyde followed by Wolff-Kischner reduction proved to be more successful. (+)-Dihydrofenchyl alcohol was oxidised according to the method of Bowers et al.[38] Semmler had already prepared[31] the aldehyde (61) but did not quote any analytical data. In the present case it was found that the aldehyde oxidised extremely rapidly in air and for this reason a good analysis could not be obtained. The aldehyde was immediately converted by the Huang-Minlon reduction to the saturated hydrocarbon (57) which did not give a satisfactory

analysis although its infrared spectrum was identical with that of the hydrocarbon $C_{10}H_{18}$ prepared from the diene. Furthermore, the mass spectrum of the synthetic hydrocarbon indicated the presence of impurity. Since the dihydrofenchyl alcohol analysed perfectly it appeared that the oxidation step was not entirely satisfactory. The technique was improved by using the method of Ruzicka and Liebl[39] whereby the dihydrofenchyl alcohol was oxidised by shaking in benzene solution with an acidified solution of potassium dichromate. The aldehyde formed was converted directly into its semicarbazone which, on heating with potassium hydroxide[40] yielded 1:1-dimethyl-3-isopropylcyclopentane (57). The latter analysed correctly and was in all respects identical with the hydrocarbon $C_{10}H_{18}$ obtained from the diene. Also, their cracking patterns in the mass spectrometer were identical. The refractive index of the synthetic hydrocarbon differed from that of the hydrocarbon from the diene since the former was optically active (prepared from (+)-fenchone).

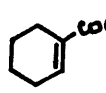
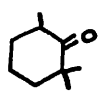
As a result of the above synthesis the carbon skeleton of the diene is firmly established and from the evidence previously discussed, the only possible structure is 1:1-dimethyl-4-isopropylidenecyclopent-2-ene (43).

The ketone $C_{10}H_{18}O$, eluted from the original chromatogram of the reaction product (page 24) with ether,

and purified via the oxime, showed no selective absorption in the ultra-violet. However, the ultra-violet spectrum of the 2:4-dinitrophenylhydrazone was comparable with that of 2:6:6-trimethylcyclohexanone (cf. Table 7) and indicated that the carbonyl group was not conjugated.

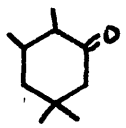
Table 7

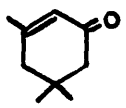
Ultra-violet spectra of 2:4-dinitrophenylhydrazones.

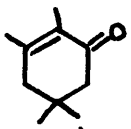
Parent Ketone	λ_1 max, mμ (ε_1 max)	λ_2 max, mμ (ε_2 max)	λ_3 max, mμ (ε_3 max)
 54	228 (15,500)	280 (13,000)	377 (24,000)
 58	230 (18,000)	277 (21,000)	360 (24,000)
 58	230 (14,700)	265 inflection (8,700)	362 (22,300)
Ketone $C_{10}H_{18}O$	229 (18,700)	265, inflection (10,500)	361 (23,200)

The infrared spectrum of the ketone confirmed that it was a cyclohexanone (ν_{max} 1705 cm.$^{-1}$, and no absorption corresponding to unsaturation) and the most probable

structure appeared to be 2:3:5:5-tetramethylcyclohexanone (62). The ketone was converted into the corresponding α,β-unsaturated ketone by bromination and subsequent dehydrobromination with 2:4-dinitrophenylhydrazine in acetic acid solution (Mattox-Kendall reaction[41]).


(62)


(63)


(64)

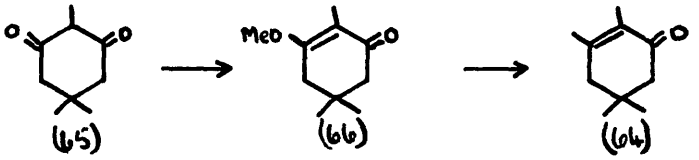
Conia, by methylation of isophorone (63) had prepared[42] 2:3:5:5-tetramethylcyclohex-2-enone (64) and confirmed its structure by degradative experiments. However, despite this, the ultra-violet spectrum which he records (Table 8) suggests that the compound might be impure (ε_{max} lower than for isophorone).

Table 8

	λ_{max} mu	ε max
Isophorone (63)	236	12,300
Monomethyl-isophorone (64)	247	9,600

The ketone $C_{10}H_{18}O$ would be established as having structure (62) by a direct correlation between it and the known unsaturated ketone (64). However, for the reasons mentioned above an alternative unambiguous synthesis of the latter was desirable.

Monomethyldimedone (65) was converted to its enol ether (66) but attempts to convert the latter to the α,β-unsaturated ketone (64) by reaction with methyl magnesium iodide at room temperature were unsuccessful.



Eschenmoser had described the reaction of lithium acetylide with a similar type of enol ether[43] and under the same conditions compound (66) gave a yield of 30% of 2:3:5:5-tetramethylcyclohex-2-enone (64). When the enol ether (66) was treated with the Grignard reagent under vigorous conditions (heating the solution under reflux for 6 hrs.) a yield of 55% of pure 2:3:5:5-tetramethylcyclohex-2-enone [λ_{max} 244 , (ε_{max} 15,200)] was obtained. The 2:4-dinitrophenylhydrazones of the latter, of Conia's ketone[44] and of the α,β-unsaturated ketone prepared from the unknown ketone by the Mattox-Kendall reaction (see page 34) were all identical thereby establishing the

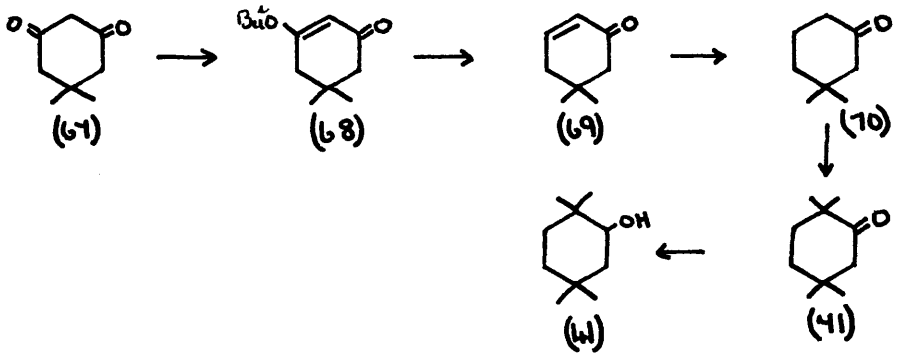
structure of the ketone $C_{10}H_{18}O$ as (62).

Attempts to prepare the saturated ketone (62) from 2:3:5:5-tetramethylcyclohex-2-enone by hydrogenation of the latter in ethanol solution over Adam's catalyst were unsuccessful since the ketone group appeared to be reduced while the double bond remained intact.

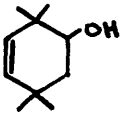
The alcohol was eluted from the chromatogram of the original reaction mixture (see page 24) with methanol-ether mixtures. The infrared spectrum of the compound indicated the presence of a hydroxyl group and a cis double bond (see page 65). The unsaturated alcohol was purified as its monoacidphthalate and, owing to the small quantities available this was reduced catalytically. The only catalyst to effect reduction was platinum oxide with the result that the hydrogen uptake was far in excess of 1 mol. (presumably owing to hydrogenation in the phthaloyl part of the molecule). Hydrolysis of the reduction product yielded a crystalline saturated alcohol $C_{10}H_{20}O$ purified via its mono-acid phthalate. The structure of this compound was confirmed as being 2:2:5:5-tetramethylcyclohexanol by its synthesis from dimedone.

Dimedone (67) was converted to its isobutyl enol ether (68) which was reduced with lithium aluminium hydride to

5:5-dimethylcyclohex-2-enone (69). The latter was hydrogenated in ethanol solution over 10% palladised charcoal to give 3:3-dimethylcyclohexanone (70) which was methylated with methyl iodide and sodamide yielding 2:2:5:5-tetramethylcyclohexanone (71) readily purified by crystallization of its semicarbazone. The ketone (71) on reduction with lithium aluminium hydride gave 2:2:5:5-tetramethylcyclohexanol (41)* identical with the saturated alcohol $C_{10}H_{20}O$ described above.



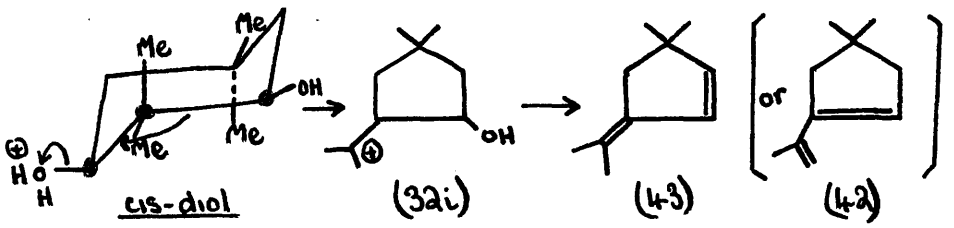
With the structure of the saturated alcohol established it follows that the unsaturated alcohol obtained from the dehydration of either diol must be 2:2:5:5-tetramethyl-cyclohex-3-enol (72).



* This compound has previously been reported by Hirsjarvi[16] but the constants for the compound itself and for its monoacid phthalate do not agree with those found for compound (41).

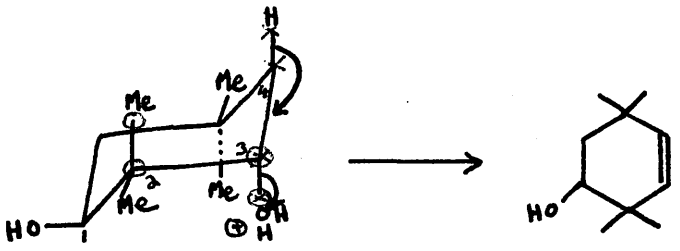
The structures of all the products arising from the dehydration of cis- and trans-2:2:5:5-tetramethylcyclohexane-1:3-diol having now been established, the mechanism of the reaction may be discussed. Since the composition of the oil obtained from the dehydration of either diol is not the same the stereochemistry of the molecule must affect the course of the dehydration.

In the cis-diol both hydroxyl groups are equatorial and from a symmetrical molecule such as this it would be expected that dehydration would give rise to a fairly homogeneous product, as was found. The environment of the hydroxyl group is similar to that of the equatorial 3-hydroxyl group in triterpenoids and thus, dehydration, accompanied by ring contraction involving the three coplanar centres marked thus • and either hydroxyl group would be expected[9].



The first step would be a concerted one involving removal of the hydroxyl group and migration of the C_2-C_3 bond to give the carbonium ion (32i) which would then eliminate a proton and dehydrate to give the diene (43). The alternative diene (42) was not found in the dehydration products.

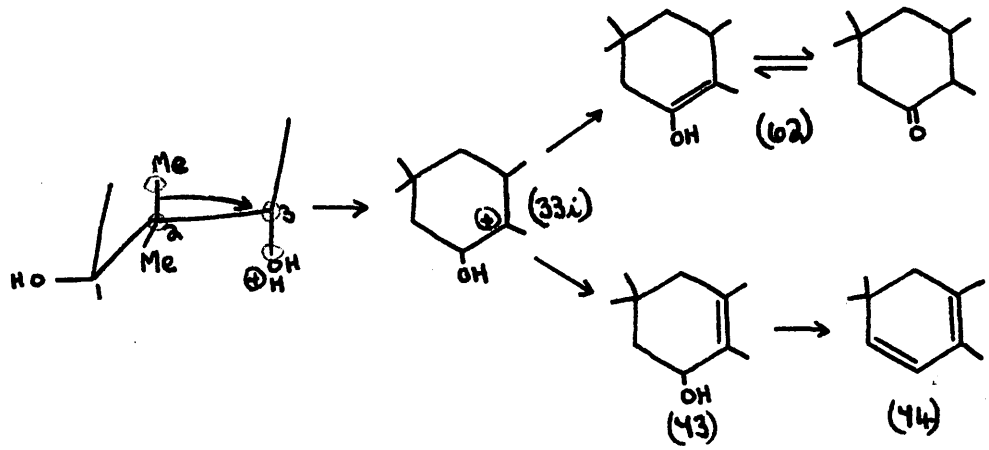
In the case of the trans-diol one hydroxyl group is axial and the other equatorial and protonation of either of these groups would give rise to different products. Dehydration involving the equatorial hydroxyl group would yield the diene as described above. There are two "four-body planar systems" which might participate in dehydrations involving the axial hydroxyl group; one includes the hydrogen atom on C_4 (marked ×) and the other the methyl group on C_2 (marked ○). Normal 1:2-elimination of water between carbon atoms 3 and 4 would give rise to 2:2:5:5-tetramethylcyclohex-3-enol.



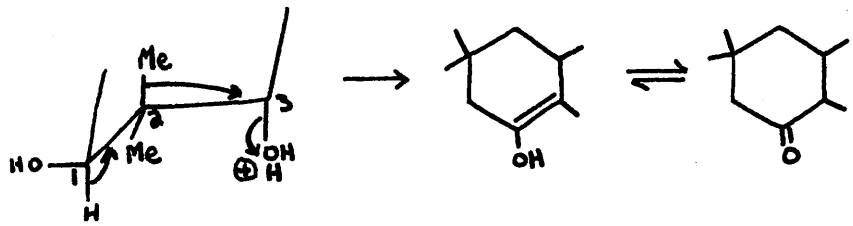
trans-diol

(42)

Removal of the hydroxyl group and simultaneous migration of the methyl group on C_2 could give the carbonium ion (33i) which by elimination of a proton would yield the ketone (62) or the unsaturated alcohol (73) and subsequently the corresponding diene (74).

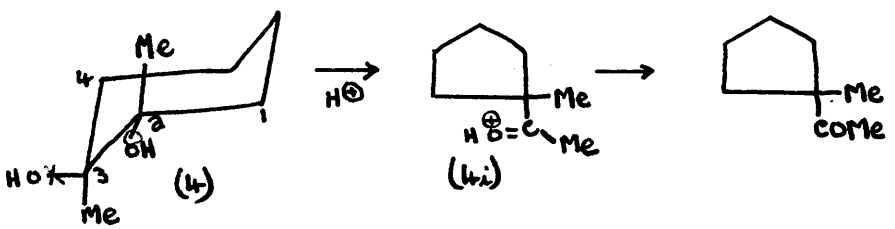


Since neither the diene (74) nor the alcohol (73) was isolated it must be assumed that ketone formation is the driving force in the elimination of a proton from the carbonium ion (33i) or alternatively, the fact that the hydrogen on C_1 is antiparallel to the migrating group makes it possible for the complete rearrangement to be concerted.



Small amounts of the ketone (62) and unsaturated alcohol (72) formed in the dehydration of the cis-diol may be regarded as arising from reactions involving the diol in the "less stable" diaxial conformation.

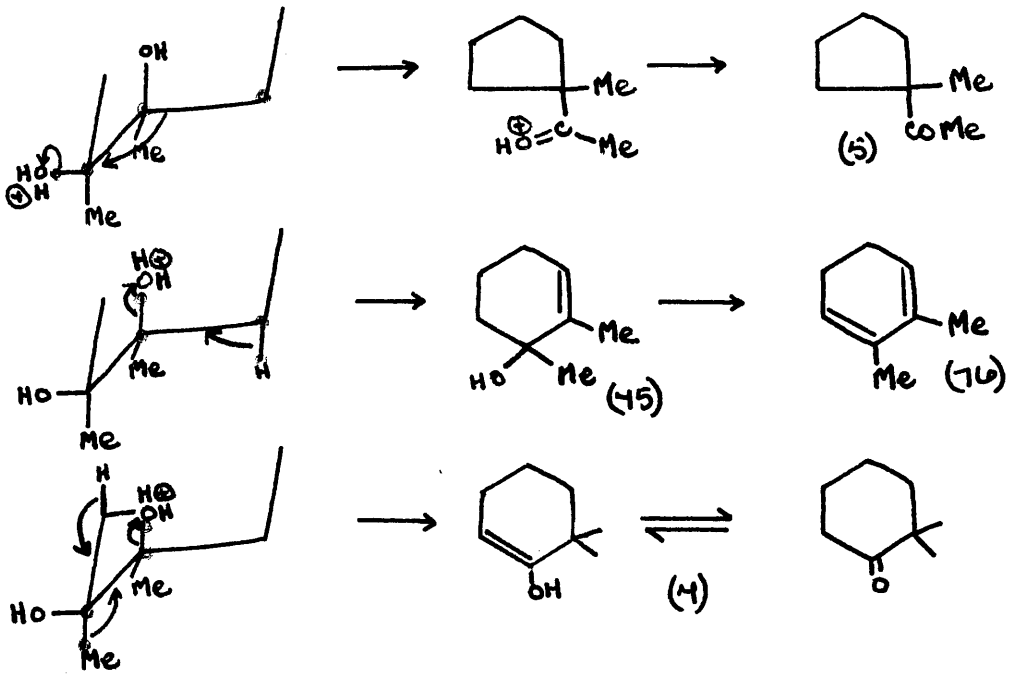
It is of interest to discuss previous results in the light of these findings. Trans-1:2-dimethylcyclohexane-1:2-diol (4) would probably exist in the conformation in which the hydroxyl groups are hydrogen bonded and diequatorial.



The hydroxyl groups marked × and ○ are coplanar with carbon atoms 1,2 and 3,4 respectively and protonation of either of these groups would be accompanied by rearrangement to give the oxonium ion (4i) and hence 1-acetylmethyl-cyclopentane (as was found experimentally)[3].

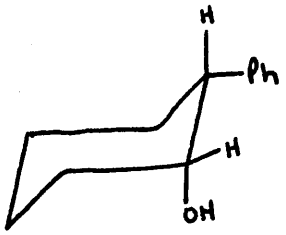
In the cis-diol there are three "four body planar systems" involving hydroxyl groups and the formation of 1-acetymethylcyclopentane (5), 1:2-dimethylcyclohex-2-enol (75), [and subsequently the corresponding diene (76)], and 2:2-dimethylcyclohexanone (7) might be anticipated from dehydrations and rearrangements

involving the three coplanar systems (marked ▾).

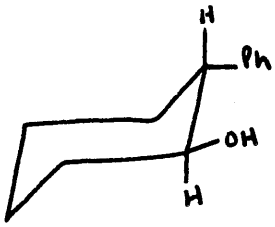


As already indicated, the product from this dehydration has variably been reported as being 1-acetyl-1-methylcyclopentane and 2:2-dimethylcyclohexanone. From the theoretical considerations, a mixture of these compounds with smaller proportions of by-products are to be expected and a thorough reinvestigation of this reaction is called for.

Recently it has been shown that trans-2-phenylcyclohexanol on dehydration with phosphoric acid yields 52% of ring contracted substances while the cis-diol gives only cyclohexyl compounds[45,46]. These results have been adequately explained on the basis of conformations (77) and (78) for the cis- and trans-alcohols respectively.

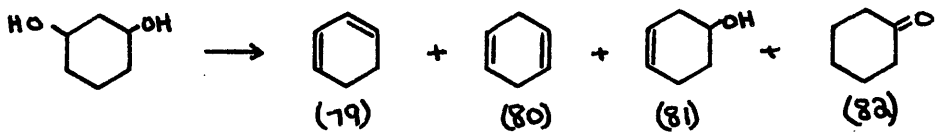


(77)



(78)

Brutcher and Cenci[47] have recently dehydrated cis- and trans-cyclohexane-1:3-diol and report that both isomers give the same yields of products (79), (80), (81) and (82), and no open chain aldehyde.

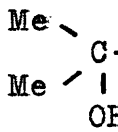


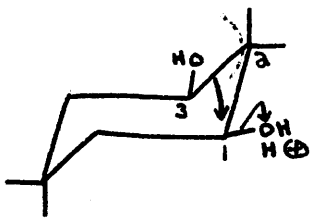
(79) (80) (81) (82)

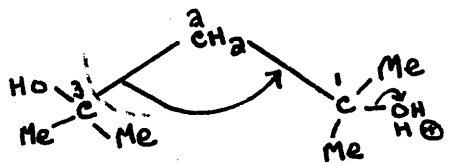
It appears, from the reactions of cyclic 1:3-diols that a different mechanism is operative in their dehydrations to that in open chain diols. There are two possible explanations of this anomaly:-

(a) The "oxide ring mechanism" for the dehydration of aliphatic 1:3-diols[11,13] is correct and hence in alicyclic 1:3-diols the formation of this "transition state oxide ring" would be much more difficult* and the reaction would proceed by a different mechanism (this was suggested by English and Brutcher[2] although corroborative experimental evidence had been lacking).

* The preparation of a 1:3-epoxycyclohexane has been reported only once[49].

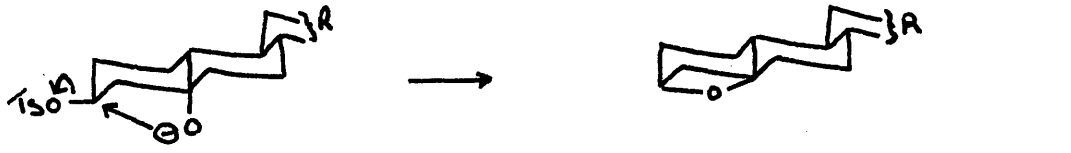
(b) What seems to be equally probable is that the mechanisms of the dehydrations of the two types of diol are very closely related. Thus both rearrangements could involve removal of the hydroxyl and simultaneous migration of the C_2-C_3 pair of electrons. In the cyclic diol however the C_2-C_3 bond would rupture at C_2 while in the open chain diol the break would be at C_3. This could be due to the fact that a rearrangement of the open chain diol analogous to that of the cyclic diol would involve migration of the bulky  grouping.





It has been shown that a steroidal 1:3-diol monotosylate of favourable conformation (-OTs,e; -OH,a) reacts with base to give a 1:3-epoxide [scheme (a)] and also an unsaturated ketone [scheme (b)][48,49].

Scheme(a)



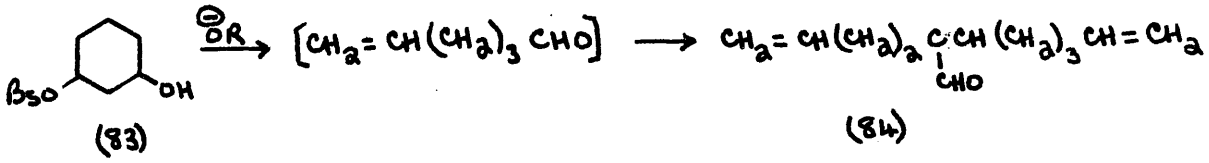
$R = C_{16}H_{30}$

Scheme(b)

It was indicated that "electronically the reaction [scheme (b)] is analogous to the acid-catalysed cleavage of 1:3-diols into ketones and olefins."

It is doubtful however whether a parallel may be drawn between the intramolecular nucleophilic rearrangement of the monotosylates and the essentially electrophilic cleavage of the diols. Certainly there seems to be little ground for comparison in the simple cyclohexane series since both cis- and trans-cyclohexane-1:3-diol give cyclohexanone as the only carbonyl product from their dehydrations, while trans-cyclohexane-1:3-diol mono-p-bromobenzenesulphonate [(83) Bs = benzenesulphonyl] with base cleaves to give an open

chain aldehyde formulated as (84).



(83) (84)

A comparison between the mode of dehydration of cholestane-3:5-diol and the rearrangement of its monotosylate [scheme (b) [49]] would determine whether a similar mechanism is operative in the two reactions.

EXPERIMENTAL

Dimedone (5:5-Dimethylcyclohexane-1:3-dione). Dimedone was prepared from mesityl oxide (100 g.) and diethyl malonate (170 g.) according to the method of Shriner and Todd[50]. Pure dimedone (75 g.) was crystallized from acetone as needles m.p. 148-149.5°.

2:2:5:5-Tetramethylcyclohexane-1:3-dione. 2:2:5:5-Tetramethylcyclohexane-1:3-dione was prepared from dimedone (100 g.) and methyl iodide (60 ml.) by the method of Halsall and Thomas[18]. The ethereal extract of mono- and dimethyldimedone was shaken with 10% aqueous sodium carbonate and the latter extract acidified with dilute hydrochloric acid to give a solid precipitate of crude 2:5:5-trimethylcyclohexane-1:3-dione.

The ether extract was evaporated to dryness and the residue steam distilled. The pure 2:2:5:5-tetramethylcyclohexane-1:3-dione (12.7 g.) crystallized from light petroleum (b.p. 40-60°) as needles m.p. 96-97°.

The dried, crude 2:5:5-trimethylcyclohexane-1:3-dione (61 g.; m.p. 130-133°) was methylated (cf.[18]) and the dimethyldimedone isolated with ether. Any alkali soluble material was removed with sodium carbonate solution. The pure 2:2:5:5-tetramethylcyclohexane-1:3-dione (33 g.) was obtained as before as needles m.p. 97-98°.

cis- and trans-2:2:5:5-Tetramethylcyclohexane-1:3-diol. Lithium aluminium hydride reduction of 2:2:5:5-tetramethylcyclohexane-1:3-dione. A suspension of lithium aluminium hydride (6 g.) in dry ether (1 litre) was heated (2 hrs.) under reflux, the returning condensate passing through a thimble containing 2:2:5:5-tetramethylcyclohexane-1:3-dione (16.8 g.). Water, followed by dilute sulphuric acid was added to the cooled reaction mixture which was then extracted with ether. The aqueous layer was extracted with two 100 ml. portions of ether and the combined ether extracts evaporated to 500 ml. and left to stand for 3 hrs.

2:2:5:5-Tetramethylcyclohexane-1:3-diol (2.9 g.), diol A, separated as needles m.p. 204-205°. Concentration of the ether extract to 250 ml. yielded a further crop of diol A, purified by recrystallization from ether as needles (0.8 g.) m.p. 206-207°. When the ethereal mother liquors were evaporated to dryness an oil (10.9 g.) remained, which solidified on standing.

Benzoylation of the Residue from Diol A. The semicrystalline residue (10.9 g.) was dissolved in pyridine (100 ml.) and benzoyl chloride (20 ml.) added slowly with stirring and cooling. After standing overnight, the mixture was poured into ice-water and extracted twice with ether.

The ether solution was washed, three times with 10% hydrochloric acid, once with 10% sodium carbonate solution, and finally with water, dried and the solvent removed. The crude dibenzoate was chromatographed on a column of alumina (500 g.). The eluants were, light petroleum (b.p. 60-80°), light petroleum-benzene mixtures, benzene, ether and methanol. A homogeneous crystalline dibenzoate (14.9 g.), diol B dibenzoate, m.p. 114-115° was eluted first, using finally a light petroleum-benzene mixture (1:1). The only other material eluted from the column was an oil.

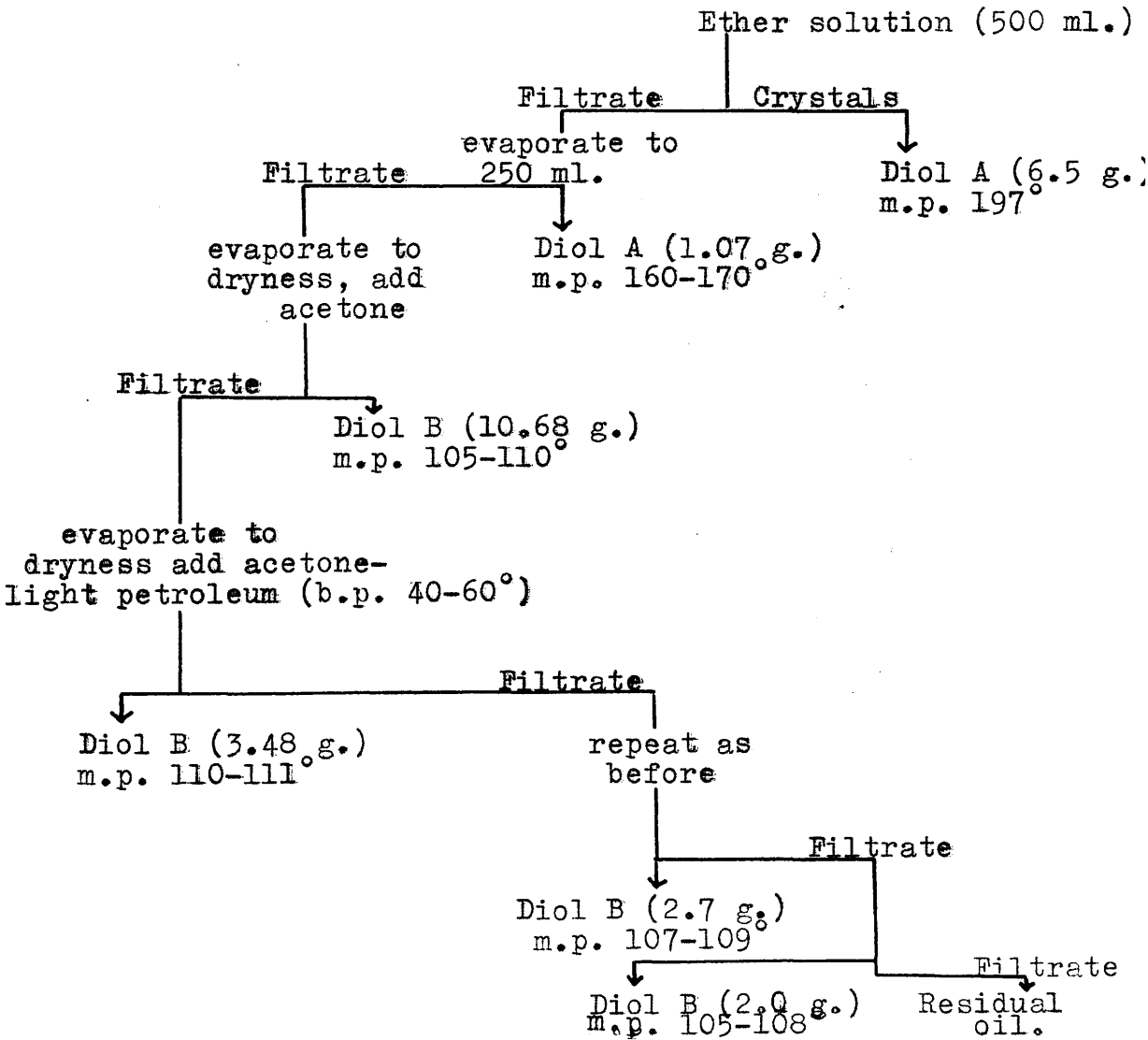
Hydrolysis of Diol B Dibenzoate. Potassium hydroxide (12 g.) was dissolved in water (minimum amount) and the dibenzoate (14.7 g.) added, followed by the minimum quantity of methanol required for complete dissolution (200 ml.). The solution was heated (6 hrs.) under reflux, the methanol removed, and the residue extracted six times with ether. Diol B, obtained from the dried etner extract was crystallized from acetone-light petroleum (b.p. 40-60°) as cubes (3.7 g.) m.p. 110-112°.

Each of the above crystalline compounds on admixture with an authentic specimen gave no m.p. depression[51].

Separation of Diols A and B by Crystallization. Dimethyldimedone (37.8 g.) was reduced with lithium aluminium

hydride as previously described and the ether solution of the diols concentrated to 500 ml. The procedure for fractional crystallization of the diols is given below. The combined diol A fractions were recrystallized from acetone-benzene to give pure diol A as needles (9.3 g.) m.p. 205-206°. Similarly the crude diol B fractions on recrystallization from acetone-light petroleum (b.p. 40-60°) gave pure diol B as cubes (17.5 g.) m.p. 109-110°.

Fractional Crystallization of Diols A and B.



Diol A Di(hydrogen Phthalate). Diol A (1 g.) and phthalic anhydride (1.8 g.) in pyridine (3 ml.) were heated (3 hrs.) on the steam bath, set aside overnight, poured into aqueous sodium carbonate and extracted three times with ether; the aqueous layer was acidified with concentrated hydrochloric acid and the product isolated in the usual way with ether was recrystallized from acetone-light petroleum (b.p. 40-60°) giving tne pure acid phthalate as prisms (1.6 g.) m.p. and mixed m.p. 212-213°[51].

Diol B Di (hydrogen Phthalate). This derivative was prepared by the method given above and was recrystallized from acetone-light petroleum (b.p. 40-60°) as prisms m.p. and mixed m.p. 193-194°[51].

Dibenzoates of Diols A and B. The dibenzoate of diol B (m.p. 114-115°) has already been described.

The dibenzoate of diol A was prepared from the high melting diol in the usual manner and was recrystallized from methanol as plates m.p. and mixed m.p. 110-111°[51].

(-)-Menthoxyacetylchloride was prepared from (-)-menthoxyacetic acid (25 g.) and thionyl chloride (65 g.; 39.6 ml.) as described in Organic Syntheses, Coll. Vol. III page 547. The pure acid chloride (23.6 g.), b.p. 145-150°/14 mm.

$[\alpha]_D^{16}$ -84.92° was obtained by distillation.

Diol A Bis-(-)-menthoxyacetate. (-)-Menthoxyacetyl chloride (2.7 g.) was added slowly to a cooled solution of diol A (1 g.) in pyridine (4 ml.) and the whole kept overnight. The mixture was poured into water and the organic material extracted with ether and worked up as in the preparation of the dibenzoates. On cooling the residue in acetone-carbon dioxide a solid formed which was crystallized from hexane and recrystallized from acetone-methanol as prisms (2.07 g.), m.p. 79-80°, $[\alpha]_D^{19}$ -71.69° (c 1.1) (Found: C, 72.07; H, 11.06%. $C_{34}H_{60}O_6$ requires C, 72.30; H, 10.71%). The theoretical values for the monoester $C_{22}H_{40}O_4$ are C, 71.69; H, 10.94% which also agree with the observed values. However the infrared spectrum of the ester (nujol mull) showed no absorption in the hydroxyl region and an ester band at 1743 $cm.^{-1}$ indicating that the compound was in fact the diester. The rotation of the compound did not change on repeated crystallization from acetone-methanol.

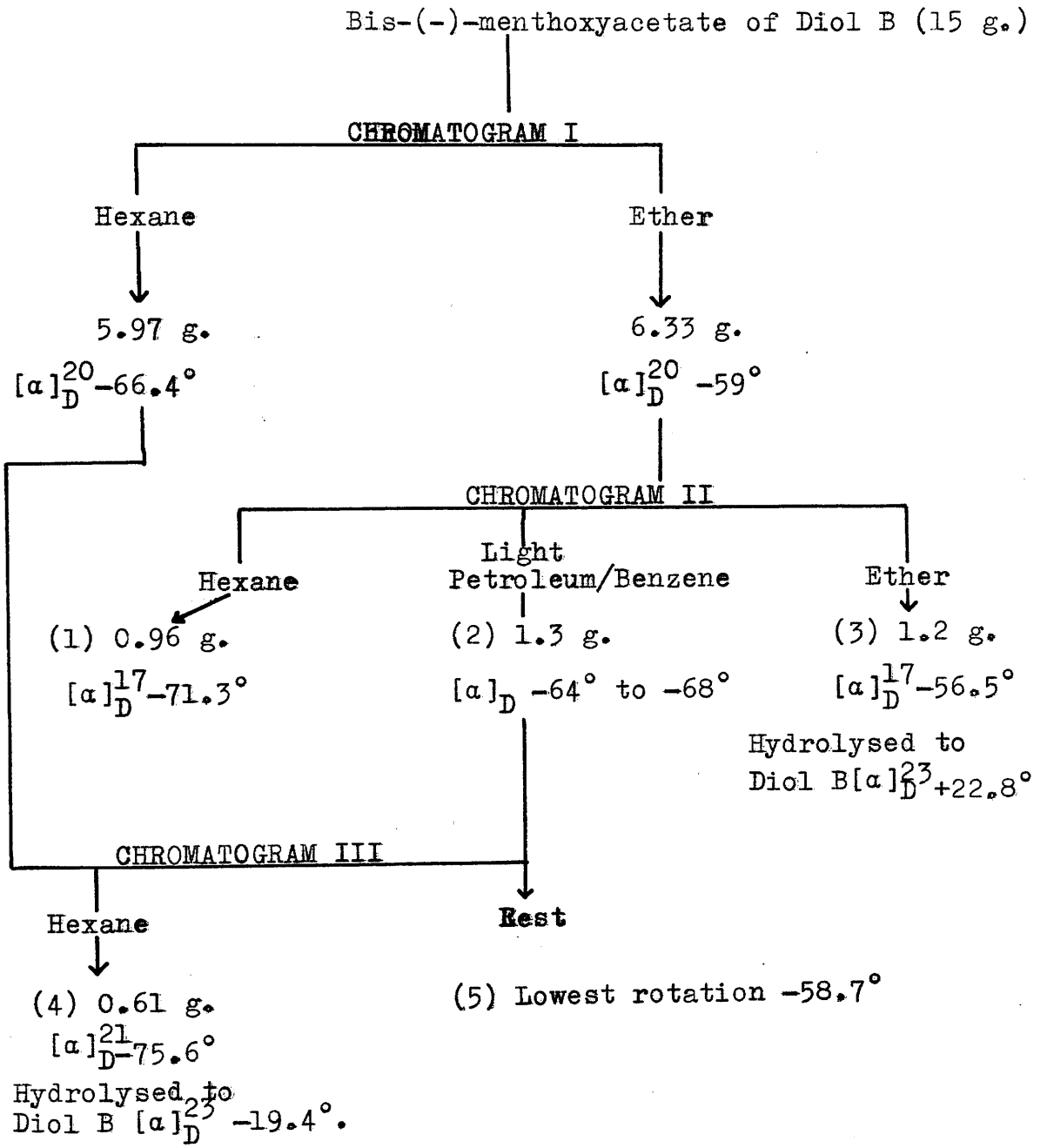
Hydrolysis of Diol A Bis-(-)-menthoxyacetate. The ester (0.25 g.) was hydrolysed with aqueous-methanolic potassium hydroxide and the product crystallized from chloroform. Diol A was thus obtained as needles, m.p. 204-207°, rotation zero.

Diol B Bis-(-)-menthoxyacetate. Diol B (6 g.) in pyridine (25 ml.) was treated with (-)-menthoxyacetylchloride as described for diol A. The brown, oily product was purified by chromatography on alumina yielding a colourless oil (15.5 g.), b.p. 210°/0.1 mm. (Found: C, 72.6; H, 10.7%). The infrared spectrum (liquid film) showed no absorption in the hydroxyl region and an ester band at 1743 $cm.^{-1}$.

The above mixture of diastereoisomeric bis-(-)-menthoxyacetates (15 g.) was chromatographed on alumina; elution with n-hexane gave a viscous oil (5.97 g.), $[\alpha]_D^{20}$ -66.37°, and elution with ether gave a second viscous oil (6.33 g.), $[\alpha]_D^{20}$-59.02°. The ether eluate was rechromatographed on alumina and from similarities in the rotation of successive eluates they were combined into three main fractions: (1) 0.96 g., $[\alpha]_D^{17}$ -71.3°; (2) 1.3 g., $[\alpha]_D^{17}$ -64° to -68°; (3) 1.20 g., $[\alpha]_D^{17}$ -56.5°. Fraction (2) was combined with the original hexane eluate and the whole rechromatographed on alumina, and from the similarities in the rotation of successive fractions two main eluates were collected: (4) 0.6 g., $[\alpha]_D^{21}$ -75.6°; (5) 3.2 g., $[\alpha]_D$ -74° to -58.7°. The chromatography of the diastereoisomeric bis-(-)-menthoxyacetates is represented diagramatically on page 55. Fraction (4) set to a wax, m.p. 59° which

could not be crystallized; on distillation one diastereoisomer of the bis-(-)-menthoxyacetate of diol B, b.p. 210°/0.1 mm. $[\alpha]_D^{21}$ -76.5° (c 0.9) was obtained (Found: C, 72.9; H, 10.8%). The infrared spectrum (liquid film) was identical with that of the original mixture. Fraction (3) set to a wax m.p. 59° which could not be crystallized, but distillation gave the other diastereoisomer of the bis-(-)-menthoxyacetate of diol B b.p. 210°/0.1mm., $[\alpha]_D^{24}$ -54.5° (c 1.1) (Found: C, 72.2; H, 10.8%). The infrared spectrum (liquid film) was identical with that of the original mixture and with that of the other diastereoisomer.

Separation of the Bis-(-)-menthoxyacetate of Diol B into Diastereoisomers - Graphical Representation.



(+) and (-)-Form of Diol B. Hydrolysis of the ester diastereoisomer, $[\alpha]_D^{21}$ -76.5° (0.18 g.) with aqueous-methanolic potassium hydroxide gave crystals (0.018 g.); these on sublimation gave (-)-diol B, m.p. 134-137° -19.4° (c 0.5) (Found: C, 69.6; H, 11.5%). The infra-red spectrum in CCl_4 was identical with that of the racemic diol B.

Hydrolysis of the diastereoisomer, $[\alpha]_D^{21}$ -54.5° (0.633 g.), gave a crystalline product (0.096 g.) which on sublimation gave (+)-diol B, m.p. 125-126°, $[\alpha]_D^{23}$ + 22.8° (c 0.9) (Found: C, 69.7; H, 11.7%). The infrared spectrum in CCl_4 was identical with that of (-)-diol B.

Dehydration of cis- and trans-2:2:5:5-Tetramethylcyclo-hexane-1:3-diol.

General method: The powdered diol (4 g.) was intimately mixed with powdered, freshly fused potassium bisulphate (8 g.) and kieselguhr (2 g.). The mixture, packed in a combustion tube, was covered with a mixture of freshly fused potassium bisulphate (4 g.) and kieselguhr (1 g.). The tube, placed horizontally, was connected to a receiver (cooled in acetone-carbon dioxide) and the apparatus evacuated at the water pump. The end of the tube containing the reaction mixture was heated at 170-190° in an electric furnace for five hours. The receiver

was then disconnected and the reaction product purified.

Separation of the Crude Oil from the Dehydration into its Constituent Compounds.

Separations based on derivative formation (Girard's Reagent T and sodium bisulphite) were unsuccessful.

Trans-Diol - The dried reaction product (3.2 g.) in isopentane was chromatographed on alumina. Elution with isopentane gave 1:1-dimethyl-4-isopropylidene-cyclopent-2-ene (43) (1.70 g.), b.p. 28-30°/1.7 mm., n_D^{20} 1.4730 (Found: C, 87.9; H, 12.0. $C_{10}H_{16}$ requires C, 88.2; H, 11.8%), $\lambda_{max.}$ 243 mμ ($\varepsilon_{max.}$ 12,500), $\nu_{max.}$ (thin film) 1620, 1600 (w, diene system), 1370, 1360 (s, - CMe_2), 816 (s, C=C) and 768 $cm.^{-1}$ (s, cis -CH=CH-). Elution with ether gave 2:3:5:5-tetramethylcyclohexanone (62), purified as its oxime, prisms from light petroleum (b.p. 60-80°) (1.07 g.), m.p. 136-137° (Found: C, 71.0; H, 11.5; N, 8.2. $C_{10}H_{19}NO$ requires C, 71.0; H, 11.3; N, 8.3%). The latter on hydrolysis with dilute hydrochloric acid gave the ketone as a colourless oil (0.87 g.,) b.p. 52-54°/1.5 mm., n_D^{21} 1.4510. (Found: C, 77.6; H, 11.5. $C_{10}H_{18}O$ requires C, 77.9; H, 11.8%). The 2:4-dinitrophenylhydrazone crystallized from ethanol as red prisms m.p. 132-134° (Found: C, 57.4; H, 6.5; N, 16.7. $C_{16}H_{22}O_4N_4$ requires C, 57.5; H, 6.6; N, 16.8%),

$\lambda_{max.}$ 229 ($\varepsilon_{max.}$ 18,700), 265 ($\varepsilon_{max.}$ 10,500) and 361 mμ ($\varepsilon_{max.}$ 23,200). Elution with ether-methanol gave an oil from which the unsaturated alcohol (72) could be isolated.

Cis-Diol - Chromatography of the dried reaction product (2 g.) gave the diene (43) (1.8 g.), and the ketone (62) with infrared spectra identical with those of the compounds obtained from the trans-diol. A third fraction was also obtained from which the alcohol could be isolated.

Hydrogenation of the Diene $C_{10}H_{16}$. - The diene (0.88g.) in acetic acid solution over Adam's catalyst (100 mgs.) rapidly absorbed hydrogen 312 ml. [theoretical (2 mols) = 312 ml]. Neutralisation with sodium hydroxide solution, followed by distillation of the dried hydrocarbon layer gave 1:1-dimethyl-3-isopropylcyclopentane (57), b.p. 148-149°, n_D^{20} 1.4267 (Found: C, 85.2; H, 14.6. $C_{10}H_{20}$ requires C, 85.6; H, 14.4%).

Ozonolysis of the Diene $C_{10}H_{16}$ - The diene (1.0g.) in pure, anhydrous ethyl acetate (17 ml.), at -75°, was subjected to a stream of ozone. When the reaction was complete (4½ hrs.), as indicated by the tetranitromethane test, the solution was evaporated under reduced pressure (2 mm.), water (10 ml.) added and the whole heated under reflux (2 hrs.) prior to distillation. After neutralisation

of the distillate with sodium hydroxide solution (to remove any acidic material), the neutral products and water were co-distilled directly into a solution of 2:4-dinitrophenylhydrazine (2 g.) in ethanol (50 c.c.) containing concentrated sulphuric acid (20 c.c.). The crude 2:4-dinitrophenylhydrazone (1.72 g.) m.p. 94-95°, was chromatographed on a column of bentonite (120 g.) and kieselguhr (30 g.) to give, by elution with chloroform, an unidentified 2:4-dinitrophenylhydrazone (0.345 g.) m.p. 162-165° as red prisms from ethanol, and by elution with chloroform-methanol (10:1) the 2:4-dinitrophenylhydrazone of acetone (0.722 g.), yellow needles (from ethanol), m.p. 124-125° alone or admixed with an authentic specimen.

(+)-Fencholamide (58a). (+)-Fencholamide was prepared by the action of freshly prepared sodamide [from sodium (14 g.)] on fenchone (100 g.), $[\alpha]_D^{18}$ + 69.0° (c 1.45), according to Semmler's method[31]. The pure amide (125 g.) crystallized from methanol as white plates m.p. 100-101°, $[\alpha]_D^{18}$ +1.4° (c 2.09). For this substance von Braun and Jacobs[52] record m.p. 116°, and state "the amide is optically inactive;" Wallach[53] records m.p. 94° and "a low positive rotation;" Semmler[31] reports m.p. 94° and makes no mention of the rotation.

(+)-Fencholic acid (58b). A saturated solution of sodium nitrite (70 g.) in water [final total volume (150 c.c.)] was added with stirring to a cooled solution of fencholamide (125 g.) in concentrated sulphuric acid (600 c.c.). The reactants were warmed on the water bath until the evolution of nitrogen had ceased. Water was added to the cooled solution, and the products extracted with ether. The acid which was isolated by extraction with sodium hydroxide solution, acidification and extraction with ether, gave, on distillation (+)-fencholic acid (60 g.), b.p. 116-118°/0.5 mm., n_D^{21} 1.4558, $[\alpha]_D^{19}$ + 3.97 (c 8.6) (lit.,[53] b.p. 151-152°/17 mm., n_D^{20} 1.4563, $[\alpha]_D$ + 4.17).

(+)*Dihydrofenchylalcohol (59). (+)-Fencholic acid (54 g.) in dry ether (500 c.c.) was added slowly to a suspension of lithium aluminium hydride (29 g.) in dry ether (600 c.c.) and the whole heated under reflux for 2 hours. The product, isolated in the usual manner gave on fractionation dihydrofenchylalcohol (42 g.), b.p. 84°/0.5 mm., n_D^{16} 1.4560, $[\alpha]_D^{20}$ + 12.25 (c 4.65). (Found: C, 77.1; H, 12.9. Calculated for $C_{10}H_{20}O$: C, 76.9; H, 12.9%). (lit.,[31] b.p. 100°/11 mm., n_D 1.4566).

(+)-Dihydrofenchylaldehyde (61). (+)-Dihydrofenchylalcohol (5 g.) in benzene (50 c.c.) was added to a solution of potassium dichromate (5 g.) in water (55 c.c.) containing

concentrated sulphuric acid (6 g.) and the whole shaken vigorously for 4 hours in an atmosphere of carbon dioxide. Fractional distillation of the washed and dried ($MgSO_4$) organic layer gave the aldehyde (2.65 g.), b.p. 50-54°/0.5 mm., n_D^{24} 1.4460 (lit.,[31] b.p. 80-85°/10mm., n_D 1.445). The semicarbazone was obtained from benzene as white needles, m.p. 152-153° (Found: C, 62.2; H, 10.1. Calculated for $C_{11}H_{21}ON_3$: C, 62.5; H, 10.0%) (lit.,[31] m.p. 144-145°). The 2:4-dinitrophenylhydrazone crystallized from ethanol as red prisms m.p. 123-124° (Found: C, 57.6; H, 6.7; N, 16.5. $C_{16}H_{22}O_4N_4$ requires C, 57.5; H, 6.6; N, 16.8%).

(+)-1:1-Dimethyl-3-isopropylcyclopentane (57). The semicarbazone of the aldehyde (61) (3.36 g.) was mixed with potassium hydroxide (7.5 g.) in a distillation flask and heated slowly until nitrogen was evolved (200°). This temperature was maintained until all the hydrocarbon had distilled (1 hr.). Distillation of the product, after washing with dilute sulphuric acid and drying, gave the hydrocarbon (57) (1.1 g.), b.p. 148-149°, n_D^{21} 1.4240, $[\alpha]_D^{20}$+ 2.94 (c 1.46). The infrared spectra of this and the hydrocarbon $C_{10}H_{20}$ were superposable.

Bromination and Dehydrobromination of the Ketone $C_{10}H_{18}O$. The ketone (62) (0.32 g.) in acetic acid (10 c.c.) was

treated slowly with bromine (1 mol.) in acetic acid (2 c.c.). The colourless solution was treated with 2:4-dinitrophenylhydrazine (0.388 g.) also in acetic acid, and the reactants warmed on the steam bath (5 min.). The product (m.p. 173-174°), obtained by precipitation with water, gave on recrystallization from ethanol the 2:4-dinitrophenylhydrazone of 2:3:5:5-tetramethylcyclohex-2-enone (0.14 g.) as bright red plates, m.p. 175-177°, alone or admixed with an authentic specimen prepared as below (Found: C, 57.8; H, 6.1; N, 16.7. $C_{16}H_{20}O_4N_4$ requires C, 57.8; H, 6.1; N, 16.9%).

2:5:5-Trimethylcyclohexane-1:3-dione (65). The dione was prepared from dimedone (100 g.) according to the method of Halsall and Thomas[18] and was crystallized twice from ethyl acetate as plates (30 g.) m.p. 160-163°.

3-Methoxy-2:5:5-trimethylcyclohex-2-enone (66). The methyl enol ether obtained by the action[54] of excess diazomethane on 2:5:5-trimethylcyclohexane-1:3-dione, was crystallized from light petroleum (b.p. 60-80°) as white prisms, m.p. 55-58° (Found: C, 71.25; H, 9.8. $C_{10}H_{16}O_2$ requires C, 71.4; H, 9.6%).

2:3:5:5-Tetramethylcyclohex-2-enone (64).

(a) By the action of lithium methyl on the enol ether (66). Lithium (0.245 g.; 3 mol.) was added in small pieces to dry ether (10 c.c.). Methyl iodide (about 20 drops) was

added in a nitrogen atmosphere and the mixture warmed gently to induce reaction. The remainder of the methyl iodide (total weight 2.54 g.) in ether (10 c.c.) was added (30 mins.) and stirring and heating under reflux continued for 1 hour by which time all the lithium had dissolved. The enol ether (66) (2 g.), in ether (10 c.c.) was added to the lithium methyl dropwise, with stirring, the temperature being maintained between 0 and 10°. After standing overnight the solution was heated (3 hrs.) under reflux; water (5 c.c.) was added cautiously, with stirring and cooling, followed by dilute sulphuric acid (10 c.c.). The ether extract was washed with dilute sodium carbonate, water, dried ($MgSO_4$) and the ether removed. Fractional distillation of the product gave the ketone (64) (0.55 g.), b.p. 75-80°/1.7 mm. (constants, analysis and derivative given below).

(b) By the action of methyl magnesium iodide on the enol ether (66). The enol ether (66) (3.2 g.) in dry ether was added slowly to a freshly prepared solution of methyl magnesium iodide [from magnesium (1.86 g.) and methyl iodide (10.82 g.)] in dry ether (15 c.c.) and the reactants heated (6 hrs.) under reflux (previous experiments at 0° and at room temperature were unsuccessful). Dilute sulphuric acid (2.5 N) was added with cooling and the

aqueous layer thoroughly extracted with ether. The ether solution was shaken (1 hr.) with an equal volume of sulphuric acid (2.5 N), to ensure complete hydrolysis of any unchanged enol ether. Fractional distillation of the product, isolated in the usual manner, gave the ketone (64) (1.5 g.), b.p. 65-67°/1.8 mm., n_D^{19} 1.4830 (Found: C, 79.0; H, 10.6. Calculated for $C_{10}H_{16}O$: C, 78.9; H, 10.6%), $\lambda_{max.}$ 244mμ ($\varepsilon_{max.}$ 15,200) [lit.,[42] b.p. 90°/8 mm., n_D^{21} 1.4798, $\lambda_{max.}$ 247mμ ($\varepsilon_{max.}$ 9,600)]. The 2:4-dinitrophenylhydrazone crystallized from ethanol as red plates, m.p. 175-177° alone or mixed with either the derivative prepared by the Mattox-Kendall reaction (page 62) or with the derivative of Conia's ketone;[42] the infrared spectra of the three specimens were superposable.

Isolation of the Third Dehydration Product. Several combined third fractions (1.63 g.) (see page 58, the purification of the dehydration product) were chromatographed on alumina to give:- (i) by elution with light petroleum (b.p. 40-60°) a mixture (0.17 g.) of ketone (62) and an alcohol; (ii) by elution with light petroleum (b.p. 40-60°) - ether (5:1) a crystalline alcohol (0.51 g.) and (iii) by elution with ether-methanol a mixture (0.73 g.) of the alcohol and unchanged diol (identified by its infrared spectrum).

The infrared spectrum of the crystalline alcohol of m.p. 44-45°, $\nu_{max.}$ 3240 (s, -OH), 1710 (w, C=O in 6-membered rings), and 768 $cm.^{-1}$ (s, cis -CH=CH-) indicated that it was an unsaturated alcohol with a trace of ketonic impurity. The hydrogen phthalate of (72) crystallized from acetic acid as white prisms m.p. 153.5 - 154.5° (Found: C, 71.5; H, 6.85. $C_{18}H_{22}O_4$ requires C, 71.5; H, 7.3%). This derivative (0.93 g.) was hydrogenated in ethanol solution over Adam's catalyst (0.1 g.), the hydrogenation being stopped after the absorption of 3.6 mols. of hydrogen. Water (3 c.c.) and potassium hydroxide (3 g.) were added to the filtered solution and the whole heated under reflux for 3 hours. The product, isolated with the aid of ether was converted to its hydrogen phthalate, which on recrystallization from aqueous acetic acid gave the hydrogen phthalate of 2:2:5:5-tetramethylcyclohexanol as white prisms m.p. 168.5 - 170.5° (Found: C, 71.4; H, 8.1. $C_{18}H_{24}O_4$ requires C, 71.0; H, 7.95%). Hydrolysis of this derivative with aqueous potassium hydroxide (10 c.c. of 10%) and subsequent sublimation of the product gave 2:2:5:5-tetramethylcyclohexanol (41), as white prisms, m.p. 54-56° (Found: C, 76.6; H, 13.2. $C_{10}H_{20}O$ requires C, 76.9; H, 12.9%).

5:5-Dimethylcyclohex-2-enone (69)- 3-isoButoxy-5:5-dimethylcyclohex-2-enone (68) (60 g.), prepared from dimedone

(50 g.) and isobutanol (75 c.c.) by Eschenmoser's method[43], b.p. 76°/0.1 mm., n_D^{18} 1.4810 (Found: C, 73.45; H, 9.8. $C_{12}H_{20}O_2$ requires C, 73.4; H, 10.3%), in dry ether (200 c.c.) was added slowly to a suspension of lithium aluminium hydride (5 g.) in dry ether (100 c.c.) and the whole heated (1 hr.) under reflux to give, by the usual isolation procedure and fractional distillation, 5:5-dimethylcyclohex-2-enone (32 g.), b.p. 76°/16 mm., n_D^{22} 1.4699 (lit.,[55] b.p. 75°/15 mm., n_D^{20} 1.4710). The 2:4-dinitrophenylhydrazone crystallized from ethanol as red prisms, m.p. 161 - 163° (Found: C, 55.5; H, 5.35; N, 18.4. $C_{14}H_{16}N_4O_4$ requires C, 55.25; H, 5.3; N, 18.4%).

3:3-Dimethylcyclohexanone (70). The above ketone (5 g.) in ethanol (50 c.c.) was hydrogenated over a palladised charcoal catalyst (0.5 g. of 10%). Hydrogen (1 mol.) was rapidly absorbed and fractionation of the filtered solution gave the ketone (70) (3.2 g.), b.p. 44 - 45°/1.5 mm., $\nu_{max.}$ 1710 $cm.^{-1}$ (s, C=O in a 6-membered ring). The semicarbazone crystallized from ethanol as needles m.p. 193-195°. The 2:4-dinitrophenylhydrazone crystallized from ethanol as prisms m.p. 108-111° (Found: C, 54.92; H, 5.58; N, 18.50. Calculated for $C_{14}H_{18}O_4N_4$, C, 54.89; H, 5.92; N, 18.29%).

2:2:5:5-Tetramethylcyclohexanone (71) - Sodamide was prepared from sodium (1.03 g.) by the method given in Organic Reactions, Vol. VIII, p. 122. The ketone (70) (2.82 g.), in dry ether (10 c.c.) was added to the freshly prepared suspension of sodamide in dry ether (30 c.c.) and the mixture heated under reflux for 1½ hours. Methyl iodide (7.35 g.) in an equal volume of dry ether was added slowly with stirring to the cold solution, and the whole subsequently heated under reflux for 4 hours. The mixture was cooled and poured into ice-dilute hydrochloric acid mixture. The product (3.3 g.), isolated with ether in the usual manner was shown, by vapour phase chromatography to contain an impurity (probably the trimethyl compound). The semicarbazone was prepared and repeated crystallization from benzene-ethanol finally gave the semicarbazone of the ketone (71) (1.82 g.) as white prisms, m.p. 198.5–201.5°. (Found: C, 62.7; H, 10.5. $C_{11}H_{21}ON_3$ requires C, 62.5; H, 10.0%). The semicarbazone (1.82 g.) was added to dilute (5N) hydrochloric acid (20 c.c.), the mixture heated (1 hr.) under reflux and the ketone removed by steam distillation and isolated with the aid of ether to give 2:2:5:5-tetramethylcyclohexanone (71) (1.3 g.), b.p. 98°/46 mm., n_D^{19} 1.4448. (Found: C, 77.2; H, 11.65. $C_{10}H_{18}O$ requires C, 77.9; H, 11.8%). The 2:4-dinitrophenylhydrazone crystallized from chloroform–ethanol as

red plates, m.p. 169-171° (Found: C, 57.2; H, 6.65. $C_{16}H_{22}O_4N_4$ requires C, 57.5; H, 6.6%).

2:2:5:5-Tetramethylcyclohexanol (41). The ketone (71) (0.88 g.) in dry ether (10 c.c.) was added to a suspension of lithium aluminium hydride (0.5 g.) in dry ether (25 c.c.) and the whole heated (1 hr.) under reflux. The product, isolated in the usual manner, gave, on distillation 2:2:5:5-tetramethylcyclohexanol as a crystalline solid m.p. 52-54° alone or mixed with the specimen prepared above. The infrared spectra of the two specimens were superposable. The hydrogen phthalate crystallized from ethanol as white prisms m.p. 169.5-171.5° alone or mixed with the specimen obtained above (page 65). The infrared spectra of the two specimens were superposable.

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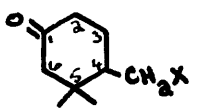
PART III

INTRODUCTION

The synthesis of α-pinene (1) via trans-norpinic acid (2) is long and arduous and a simpler route from dimedone (3) or a related compound was envisaged. The problem is essentially one of bridging carbon atoms 4 and 6 in dimedone with a $-CH_2-$ grouping to give 4:6-diketonopinane (4).

(1) (2) (3) (4) (5)

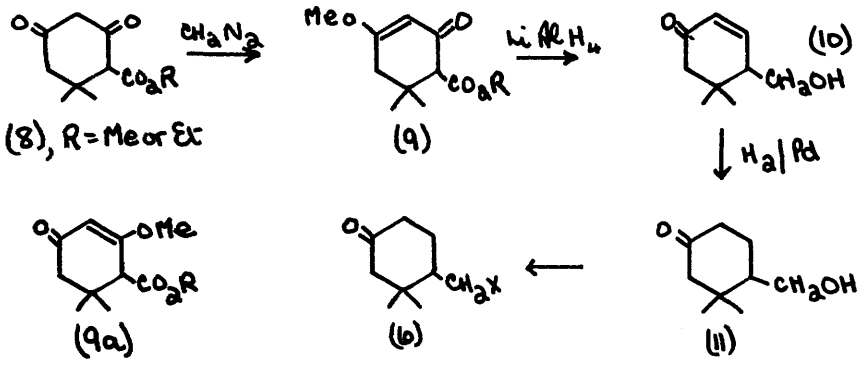
The reaction at first contemplated was one similar to that of methylene iodide on the sodium salt of Guareschi's imide[1]. However, previous attempts to carry out this reaction on Schreiber and Meisel's ester (5)[2] and more recently on dimedone[3] were unsuccessful. The alternative approach was to prepare the compound (6), the anion of which, suitably blocked in position 2, should undergo cyclisation[4] with displacement of X to give nopinone (7).



(6) (7)

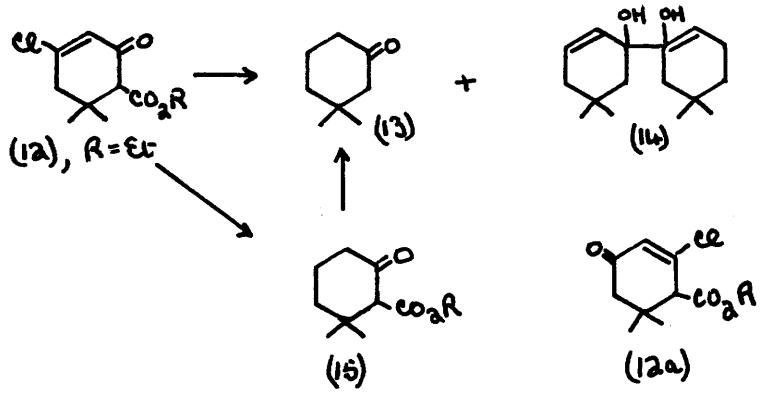
X = Br, -OTs or similar group.

It was thought that Vorlander's ester (8), an intermediate in the preparation of dimedone might be converted to the compound (6) by the following scheme:-



The course of the reactions depends on the structure of the enol ether (9) since the alternative structure (9a) would lead to different products.

Steiner and Willhalm[5] have elucidated the structure of the enol chloride (12) prepared by the action of phosphorus trichloride on Vorlander's ester.

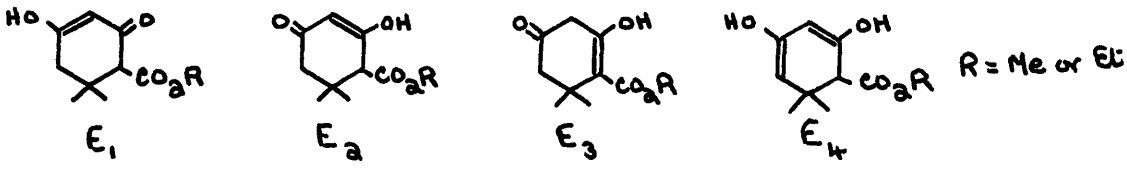


The chloride (12) on reduction with zinc dust in acetic acid solution yielded 2:2-dimethylcyclohexanone (13) and the pinacol (14). The β-ketoester (15) obtained by hydrogenation of the enol chloride gave a deep violet ferric chloride colour and was hydrolysed to the ketone (13).

These reactions showed that the alternative structure (12a) for the enol chloride was inadmissible. Thus in order to establish the structure of the enol ether of Vorlander's ester a direct correlation between it and the enol chloride (12) was necessary.

DISCUSSION

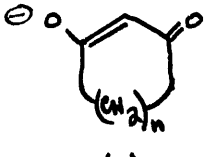
There are several possible structures (E_1 — E_4) for the enol form of Vorlander's ester.



E_1 E_2 E_3 E_4

Structure E_4 can be immediately rejected on the basis of Meek, Turnbull and Wilson's work[6] and also from the fact that the dione forms a mono-enol ether as distinct from a di-enol ether. In order to decide which of the other three structures was most probable, a study was made of the ultra-violet and infrared spectra of Vorlander's ester and related compounds.

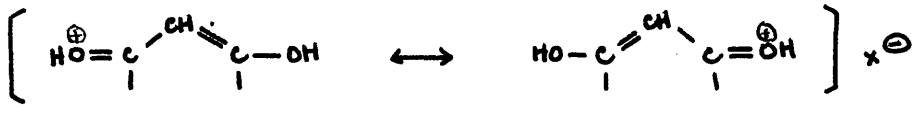
Trans-fixed β-diketones are characteristic in that the position of $\lambda_{max.}$ is dependent on concentration and shifts to longer wave lengths on dilution[7]. This has been attributed to the fact that in dilute solution there is a high concentration of the ionic species (I)[8]. As expected, the dilution effect is completely nullified by the addition of dilute acid and duplicated by the action of alkali.

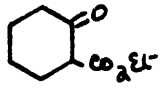


(I)

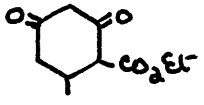
The position of $\lambda_{max.}$ for cis-fixed β-dicarbonyl compounds (acylcyclanones etc.) is dependent on pH but independent of dilution[9].

Concentrated acid has the same effect as alkali on the ultra-violet spectrum of β-diketones due to oxonium ion formation[9,10].





(16)



(17)

While Vorlander's ester* was found to exhibit the dilution effect 2-ethoxycarbonylcyclohexanone (16)[12] as expected, did not, although the ultra-violet spectrum of the latter was affected by the addition of alkali (Table 1, page 82 and Fig. 1, page 81). This implied that in Vorlander's ester enolisation was taking place between the ring carbonyl groups and not between the carbonyl and ester groups as represented in structure E_3.

The infrared spectrum of the enol ether of Vorlander's ester showed the presence of a conjugated carbonyl group, a conjugated double bond, and C-H deformation vibrations

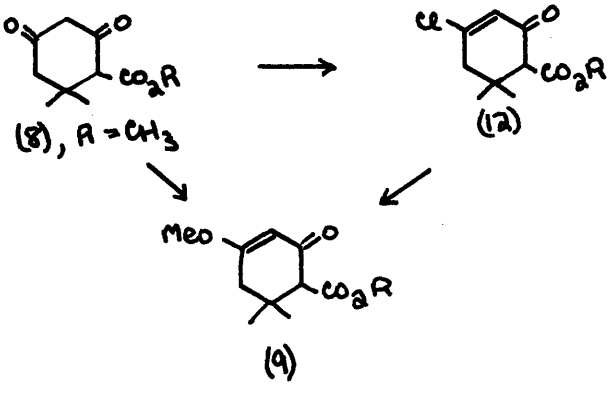
* The closely related compound, ethyldihydroorsellinate (17) was studied simultaneously.

associated with a double bond (Table 2, page 84) all of which were consistent with either formula E_1 or E_2 for the enol. It was impossible, by physical methods to determine which of these two structures was correct.

The elucidation of the structure of Vorlander's ester enol ether by chemical methods could be approached in several different ways.

Attempts to hydrogenate the enol ether in ethanol solution over Adam's catalyst were unsuccessful; no hydrogen was taken up. The enol ether was also unaffected by potassium borohydride.

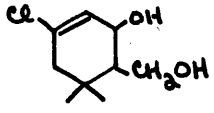
Correlation of the enol ether with the known enol chloride (12) was the other alternative. The dione (8) on treatment with phosphorus trichloride yielded the enol chloride (12), which on reaction with sodium methoxide gave an enol ether (9) identical with the compound prepared by the action of diazomethane on the dione (8).



The structure of the enol ether was thus established as being (9). The acidic character of the dione is demonstrated by these reactions. The enol ether may be regarded as a vinylogous ester and the enol chloride as the corresponding acid chloride.

Lithium aluminium hydride reduction of the enol ether both in ether and in tetrahydrofuran gave (from the infrared spectrum) a mixture of compounds.

Reduction of the enol chloride (12) with lithium aluminium hydride yielded a crystalline compound $C_9H_{15}O_2Cl$ which gave no reaction with 2:4-dinitrophenylhydrazine and appeared (from its infrared spectrum, Table 2) to have the structure (18).

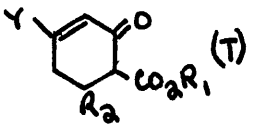


(18)

At this point it was decided that, owing to the unsatisfactory nature of the products from these lithium aluminium hydride reductions further work along this line would introduce unnecessary complications into the synthesis of the keto-alcohol (11).

From the infrared spectral data (Table 2) it was

evident that compounds of the type (T) showed three bands in the carbonyl region at 1725-1730 cm.$^{-1}$, 1650-1670 cm.$^{-1}$ and 1600-1620 cm.$^{-1}$ arising from the ester, conjugated carbonyl and conjugated double bond groupings respectively.



(T)

Y = -OMe or -Cl
R_1 = Et or Me
R_2 = $(Me)_2$ or Me

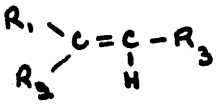
In the spectrum of the diol (13) the presence of a weak band at 1663 cm.$^{-1}$ may be associated with the non-conjugated -C=C- stretching vibration and a strong band at 3280 cm.$^{-1}$ with intramolecularly hydrogen bonded hydroxyl groups. All of these compounds show several medium peaks in the region 890 - 770 cm.$^{-1}$ associated with the grouping 

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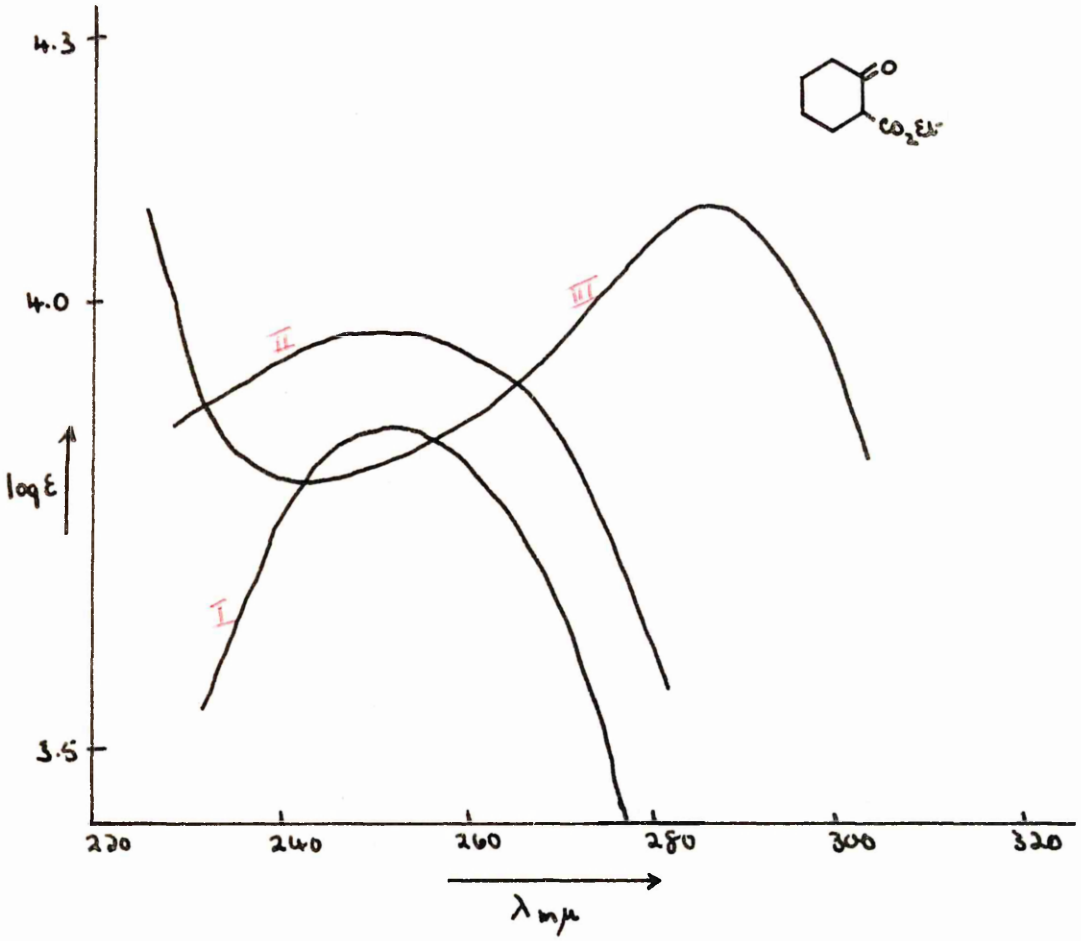
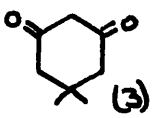
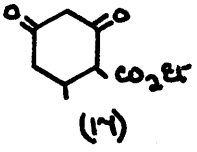
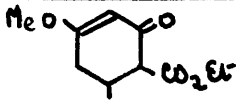
Fig 1.



I Ethanol, II Ethanol - dil. HCl, III Ethanol - dil. NaOH solution.

Table 1

Ultra-violet Spectra*

Compound	Solvent	Concentration mgs./100 c.c.	$\lambda_{max.}$, mμ ($\varepsilon_{max.}$)
 (3)	Ethanol	1.1	256 (15,900)
	"	0.55	257 (18,180) 270 (20,100) 277 (inflection)
	"	0.22	282 (25,900)
 (14)	Ethanol	2.38	255 (19,200)
	"	0.958	263 (10,080) 280 (10,420)
	"	0.479	282 (21,160)
	Cyclohexane	5.10	251 (3,502)
	Ethanol	0.782	248 (18,750)

* Determined with a Unicam spectrometer.

Table 1 contd.

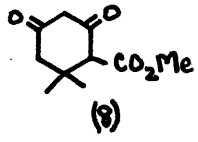
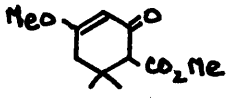
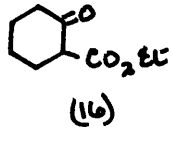
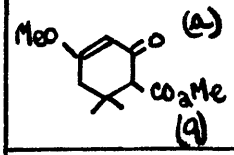
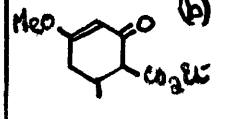
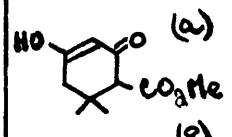
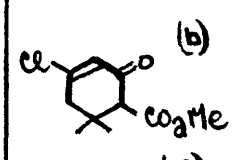
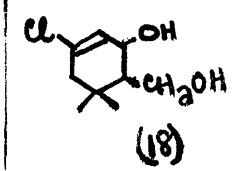
Compound	Solvent	Concentration mgs./100 c.c.	$\lambda_{max.}$, mμ ($\varepsilon_{max.}$)
 (8)	Ethanol	2.66	261 (12,400)
	"	1.064	267 (inflection) 284 (9,906)
	"	0.532	286 (22,180)
	Cyclohexane	4.05	256 (1,773)
	Ethanol	0.189	252 (17,120)
 (16)	Ethanol	0.68	252 (7,174)
	Ethanol-dil. NaOH	0.68	285 (13,150)

Table 2

Infrared Spectra*

Compound	$-CO_2R$ ($cm.^{-1}$)	>C=O, conj. ($cm.^{-1}$)	>C=C< ($cm.^{-1}$)	-C(H)=C< ($cm.^{-1}$)
 (9)	1703 s.	1650 s.	1605 s. (conj.)	889 m, 846 m, 829 m, 774 m.
 (b)	1725 s.	1650 s.	1610 s. (conj.)	886 m, 873 m, 848 m, 828 m.
 (8)	1738 s.	1590 s.	1532 s. (conj.)	940 m, 897 w, 844 w.
 (13)	1730 s.	1670 s.	1615 s. (conj.)	912 m, 887 m, 855 m, 808 m, 770 m.
 (18)	Additional peaks:	3280 s, C-OH 698 m 671 m C-Cl	1663 w.	862 w, 849 m, 794 w.

* Determined with a Perkin Elmer, Model 13, direct ratio, infrared spectrometer, using a sodium chloride prism.

(a) Nujol mull; (b) Thin film.

EXPERIMENTAL

Vorlander's Ester [(8), R = Me]. The ester was prepared from mesityl oxide (102 g.) and dimethylmalonate (141 g.) according to the method of Vorlander[11]. The dione was obtained as needles (132 g.), m.p. 99-100°, after two crystallizations of the crude product from benzene. Recrystallization from ethyl acetate-petroleum ether (b.p. 60-80°) gave the pure dione as needles, m.p. 103-104°.

Vorlander's Ester Enol Ether [(9), R = Me].

Method (a). Vorlander's ester (20 g.) was dissolved in benzene (100 c.c.). p-Toluene-sulphonic acid (0.5 g.) and dry methanol (5 c.c.) were added and the solution heated (4 hrs.) under reflux, the returning condensate being passed through silica gel to remove water. The solution was cooled, poured into saturated sodium bicarbonate solution and extracted with ether. The ether extract was washed twice with 10% sodium carbonate solution, and water, dried ($MgSO_4$) and the ether removed. Distillation of the remaining oil gave the pure enol ether (8.42 g.), b.p. 120-124°/0.5 mm., n_D^{20} 1.4950 (Found: C, 62.09; H, 7.76. $C_{11}H_{16}O_4$ requires C, 62.25; H, 7.60%).

Method (b). Vorlander's ester (10 g.) was dissolved in analar acetone (40 c.c.). Diazomethane, [from nitrosomethylurea (20 g.)] was distilled into the cooled ester solution.

The solvent and excess diazomethane were removed and the remaining oil distilled to give the pure enol ether (8.47 g.), b.p. 116-118°/0.1 mm.

Ethyldihydroorsellinate Enol Ether.

Method (a). Esterification of ethyldihydroorsellinate (17) (20 g., m.p. 85-89°) as above and distillation of the product gave the pure enol ether (10.8 g.), b.p. 134-136°/0.7 mm., n_D^{19} 1.4942. The enol ether was crystallized from light petroleum (b.p. 40-60°), as needles, m.p. 48-51°.

Method (b). The action of diazomethane on ethyldihydroorsellinate (10 g.) and distillation of the resulting oil gave the enol ether (9.22 g.), b.p. 128-130°/0.6 mm.

The Enol Chloride of Vorlander's Ester [(12), R = Me]. Vorlander's ester (10 g.) was added to phosphorus trichloride (2.54 g.) in chloroform (25 c.c.) and the solution heated (3 hrs.) under reflux. The chloroform was distilled off and ice-cold water added. The mixture was shaken, ether added and the organic layer washed three times with a total of 100 c.c. of 10% sodium bicarbonate solution, then water, dried ($MgSO_4$) and the solvent removed. Distillation of the remaining oil gave the pure enol chloride (6.84 g.), b.p. 90-92°/0.2 mm., n_D^{21} 1.4938 (Found: C, 54,69; H, 6.27. Calculated for $C_{10}H_{13}O_3Cl$:

C, 55.42; H, 6.04%), $\lambda_{max.}$ 239 mμ ($\varepsilon_{max.}$ 12,270).

Reaction of the Enol Chloride of Vorlander's Ester with Sodium Methoxide. Freshly cut sodium (0.106 g.) was dissolved in dry menthanol (5 c.c.) and the enol chloride (1 g.) in dry methanol (5 c.c.) added. The solution was stirred at room temperature for 30 mins. during which time a white solid (NaCl) separated. Water was added and the mixture extracted with ether. The product isolated from the washed and dried ether extract had an infrared spectrum identical with that of Vorlander's ester enol ether (prepared above).

Lithium Aluminium Hydride Reduction of Vorlander's Ester Enol Chloride. Lithium aluminium hydride (0.5 g.) was suspended in dry ether (20 c.c.) and the enol chloride (2 g.) in dry ether (20 c.c.) added slowly with stirring. The mixture was stirred and heated (1 hr.) under reflux. Water was added slowly, then dilute hydrochloric acid and the mixture extracted with ether. The product (18) isolated from the washed and dried ether extract, crystallized from acetone-light petroleum (b.p. 40-60°) as prisms (0.5 g.), m.p. 123-124° (decomposition) (Found: C, 56.71; H, 8.43. $C_9H_{15}O_2Cl$ requires C, 56.66; H, 7.92%).

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2. Guha and Mayuranathan, J. Indian Inst. Sci., 1932, 15, 131.
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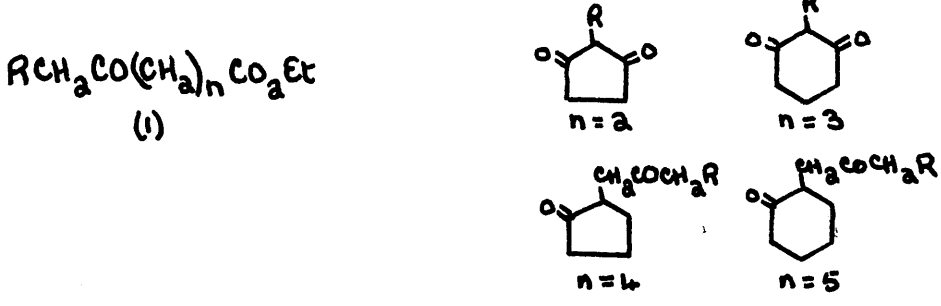
7. Bastron, Davies and Butz, J. Org. Chem., 1943, 8, 515.
8. Blout, Eager and Silverman, J. Amer. Chem. Soc., 1946, 68. 566.
9. Eistert and Reiss, Ber., 1954, 87, 1513-40.
10. Eistert, Merkel and Reiss, Ber., 1954, 87, 108-23.
11. Vorlander, Ann., 1896, 294, 300.
12. Kindly supplied by Dr. R.P.A. Sneeden.

PART III.

INTRODUCTION

Five and six membered cyclic 1:3-diones are readily available by the intramolecular Claisen condensation of the appropriate keto-ester (1)[1].

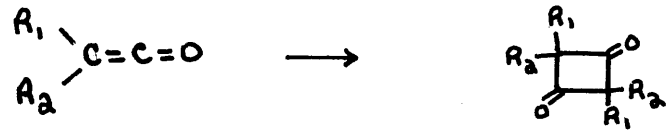


Cyclisation of the keto-ester (1) with base results in the formation of a cyclopentane- or cyclohexane-1:3-dione when n is 2 or 3 respectively (R = H or alkyl) or an acylcyclopentanone or acylcyclohexanone when n is 4 or 5 respectively (R = H or alkyl).

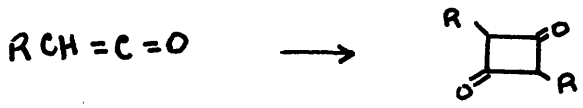
No general method has been put forward for the preparation of cyclic 1:3-diones of arbitrary ring size. It was thought that if a keto-ester were used having an activated $-CH_2-$ grouping adjacent to the keto group on the side remote from the ester grouping an intramolecular condensation would take place at this carbon atom (i.e. at C_{n+3}) irrespective of the number of intervening carbon atoms. Thus if n is 4 (R = COOEt) in the keto-ester (1), the activated $-CH_2-$ grouping would be at position 7 and the cyclisation product would be a cycloheptane-1:3-diene*.

* The synthesis of a cyclohexane-1:3-dione by this type of reaction has been reported[2].

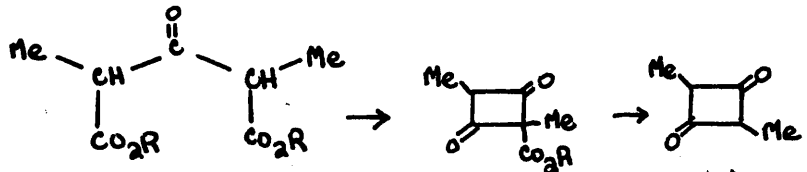
The number of cyclic 1:3-diones other than 5 or 6 membered, which have previously been prepared is very limited. Dialkylketenes were found to dimerise symmetrically to give tetraalkylcyclobutane-1:3-diones[3].



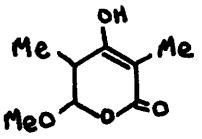
The monosubstituted ketene gave the appropriately substituted cyclobutane-1:3-dione in small yield[3].



2:4-Dimethylcyclobutane-1:3-dione (4) was also prepared by the action of cold sulphuric acid on symmetrical dimethylacetone dicarboxylic esters (2) followed by mild hydrolysis of the intermediate ester (3)[4].

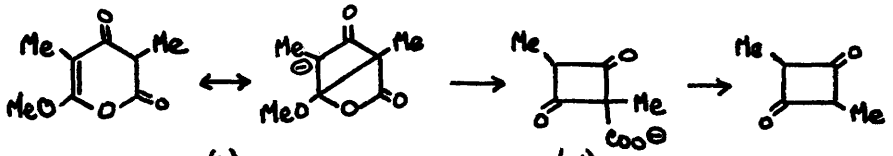


The formulation of the latter as (3) has recently been shown to be wrong[4]. The compound is in fact a pyrone with the structure (5).



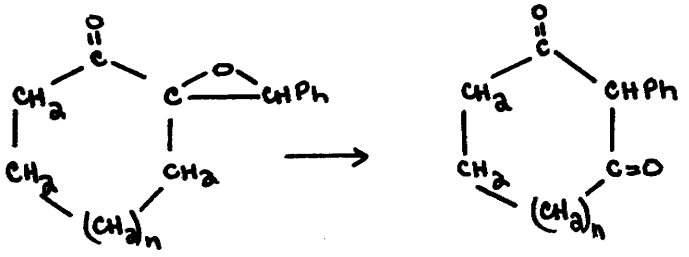
(5)

The mechanism of the conversion of this pyrone into 2:4-dimethylcyclobutane-1:3-dione has been postulated as proceeding via the ionic intermediates (6) and (7).



(6) (7)

What appears to be a general method for the preparation of cyclic 2-phenyl-1:3-diones has recently been reported by House and Wasson[5]. The appropriate α,β-epoxyketone (8) when treated with boron trifluoride etherate underwent rearrangement to give the cyclic 1:3-dione (9).



(8) a: n=0
b: n=1
c: n=2

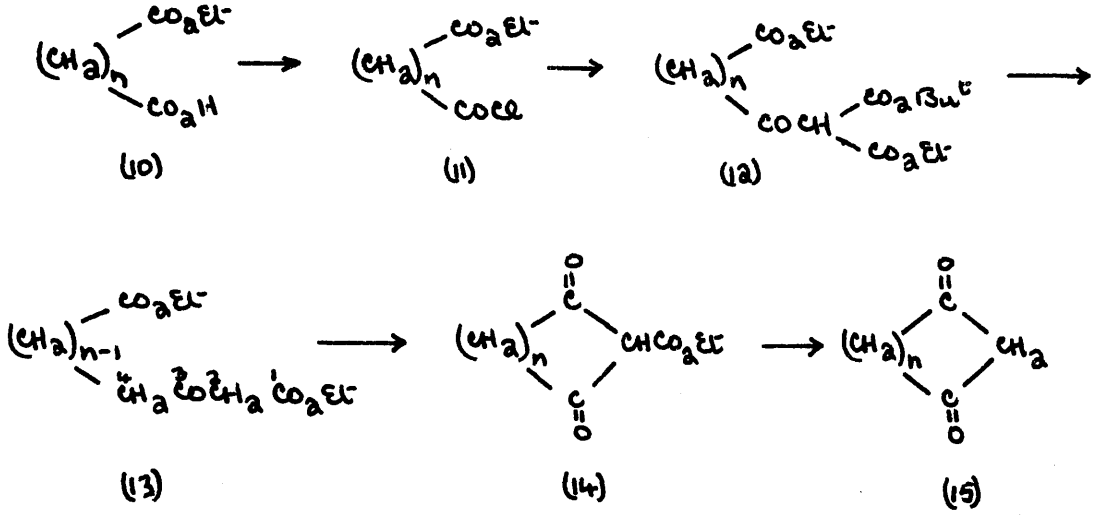
(9) a: n=1
b: n=2
c: n=3

In this way 2-phenylcyclohexane-, 2-phenylcycloheptane- and 2-phenylcyclooctane-1:3-diones (9a), (9b) and (9c) respectively were prepared. The properties of 2-phenylcyclohexane-1:3-dione were comparable with those of dihydroresorcinol but the higher 1:3-diones appeared to exist largely in the diketo rather than in the enolic forms (from ultra-violet and infrared spectra).

It is evident from the limited information available on the preparation and properties of higher cyclic 1:3-diones that a more thorough investigation of these compounds is necessary.

DISCUSSION

The proposed scheme of reactions for the synthesis of a higher cyclic 1:3-dione was as follows:-

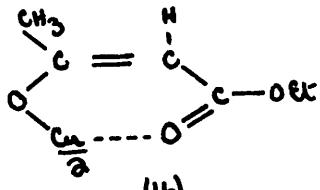


In the compound (13) the $-CH_2-$ group between the terminal ester group (C_1) and the carbonyl group (C_3) is highly reactive and intramolecular condensation should take place here rather than at the alternative $-CH_2-$ group (i.e. at C_4). It was decided to try out the scheme of reactions with the ultimate aim of synthesising cycloheptane-1:3-dione [(15), n = 4].

Condensation of ethyl chloro adipate (11) with ethyl tert-butyl malonate in the presence of magnesium ethoxide gave the triester (12) which was immediately decomposed to isobutene, carbon dioxide and 1:6-diethoxycarbonylhexan-2-one (13). The latter, at high dilution, was treated with

potassium tert-butoxide[6]. The crude reaction product was distilled and an oil $C_{10}H_{14}O_4$ (subsequently referred to as the "Dieckmann ester") was obtained in good yield; the residue on trituration with acetone gave a crystalline material $C_8H_8O_3$.

The Dieckmann ester, $\lambda_{max.}$ 310 mμ ($\varepsilon_{max.}$ 18,210) had an infrared spectrum attributable to a β-diketone system and an ester grouping (see page 11a). Dilute alkali had little effect on the position of $\lambda_{max.}$ although dilute acid caused a bathochromic shift with the simultaneous appearance of a new maximum at 253 mu**. The ester gave a copper enolate the infrared spectrum of which indicated the presence of free ester (s 1723 $cm.^{-1}$), conjugated carbonyl (s 1598 $cm.^{-1}$), and conjugated double bond (s 1502 $cm.^{-1}$) groupings. There were no strong peaks below 1040 $cm.^{-1}$ suggesting that there were no hydrogen atoms associated with the double bond in the enolate [cf. infrared spectrum of acetoacetic ester copper enolate (16)]. Since β-keto ester copper enolates [e.g. (16)] show characteristic absorption in the carbonyl region it was evident that the ester group of the Dieckmann ester (see above) was not involved in enolate formation.



(16)

$\lambda_{max.}$ cm.$^{-1}$	Group.
1600 s	conjugated double bond
1540 s	$>C=C-$ nd.
778 s	$>C=C-$ (H)

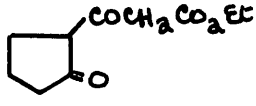
It was therefore very difficult to account for the properties of the Dieckmann ester copper enolate on the basis of a cyclic-1:3-dione structure unless it was postulated that the complex was actually a copper salt, not internally bonded.

In order to obtain more information about the structure of the Dieckmann ester the ultra-violet spectra of the parent compound and of its copper enolate were compared with those of reference compounds**. The spectra of the enolate ions of acetylcyclopentanone and acetylcyclohexanone[18] were comparable with that of the unknown ester in neutral and in alkaline solution (Figs. 2, 1, and 3). Acetylcyclohexanone in weakly alkaline solution showed two maxima at 304 and 240 mμ probably due to absorptions of the enolate ion and the enol respectively. The cis-fixed β-diketone copper enolates (Fig. 4) showed two maxima at 240-255 mμ and at 300-315 mμ while the β-keto-ester copper enolates (Fig. 5) showed only one maximum at 280 mμ with an

** For ultra-violet data and spectra, see pages 101 - 104 .

inflection at about 240 mμ. Also, it was apparent that the ultra-violet spectrum of the Dieckmann ester copper enolate was very similar to that of acetylcyclopentanone copper enolate.

These considerations, along with the infrared spectral data suggested that the Dieckmann ester was not in fact a seven-membered ring compound but more probably 2-(carboethoxy-acetyl)-cyclopentanone (17).

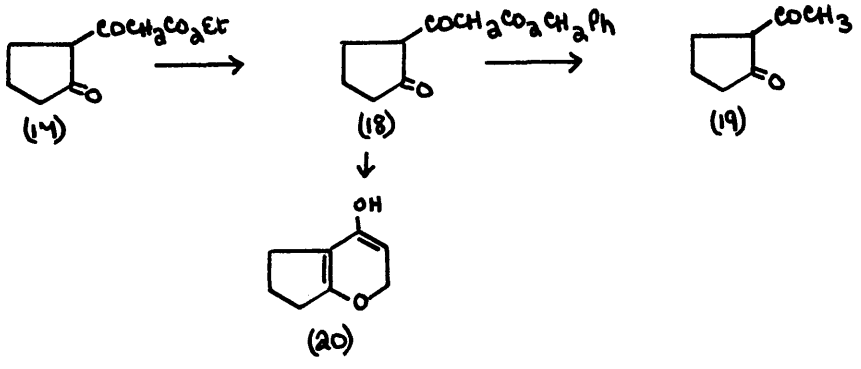


(14)

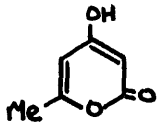
Ethylacetoacetate is readily converted into the corresponding benzyl ester by heating with benzyl alcohol[7] and a similar exchange reaction was attempted with the Dieckmann ester. The crude benzyl ester which resulted showed only a slight hydroxyl peak and strong aromatic peaks in its infrared spectrum suggesting that the exchange had actually taken place. The ester was hydrogenated in ethanol solution in the presence of 10% palladised charcoal to give a product whose ultra-violet spectrum was consistent with that of crude acetylcyclopentanone. This crude material was distilled and the infrared spectrum of the

resulting oil showed the same peaks as that of synthetic acetylcyclopentanone prepared from cyclopentanone via 1-morpholinocyclopentene.

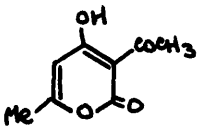
The above exchange reaction was then repeated with a view to isolating and characterising the intermediate benzyl ester. However when vacuum distillation of the crude benzyl ester was attempted only benzyl alcohol distilled leaving a residue which rapidly crystallized. The purified crystalline material was shown (infrared spectra and mixed m.p.) to be identical with the crystalline substance $C_8H_8O_3$ obtained as a by-product in the Dieckmann ester preparation (page 94). This confirmed the structure of the latter since the benzyl ester (18) would, on the one hand be hydrogenolysed to a β-keto-acid and hence to acetylcyclopentanone (19) and on the other undergo pyrolysis with the elimination of benzyl alcohol to give 4-hydroxy-5:6-trimethylene-2-pyrone (20). Furthermore the Dieckmann ester could, under the basic conditions required for its preparation undergo further cyclisation to the pyrone (20).



The ultra-violet spectrum of the pyrone (20) (fig. 6) was interesting in that alkali caused a bathochromic shift of $\lambda_{max.}$ contrary to what is normally expected for trans-fixed β-diketones (see Part II page 46). This "abnormal property" had previously been reported for triacetic lactone (21)[8].



(21)

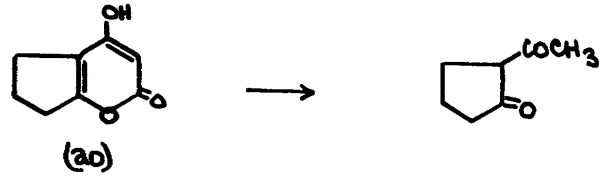


(22)

In order to compare the spectral characteristics of the pyrone (20) with those of triacetic lactone (21) the latter was prepared from dehydroacetic acid (22). The ultra-violet spectra of the two compounds (20) and (21) were very similar and alkali produced the same shifts (Figs. 6 and 7). Also the infrared spectra of each showed a triplet in the 800-900 $cm.^{-1}$ region although the carbonyl regions were not so comparable (see pages 114 and 116).

Confirmatory evidence for the structures of the Dieckmann ester (17) and the pyrone (20) was obtained by hydrolysis of the latter with dilute sulphuric acid. The product gave a copper salt which was identical with a synthetic sample of acetylcyclopentanone copper enolate

and was hydrolysed to acetylcyclopentanone. The formation of the latter from the pyrone (20) can be formulated as involving hydrolysis and decarboxylation, a reaction which has already been discussed for triacetic lactone[9].

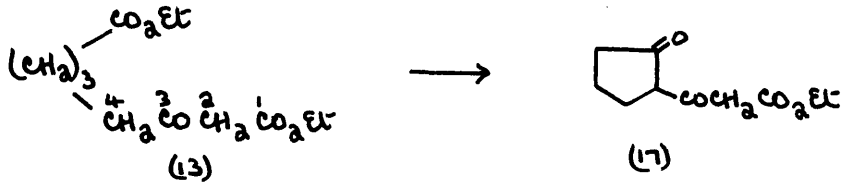


(20)

4-Hydroxy-5:6-trimethylene-2-pyrone has recently been synthesised[10] and a direct comparison of the infrared spectra of the latter[11] and of the pyrone (20) showed them to be identical.

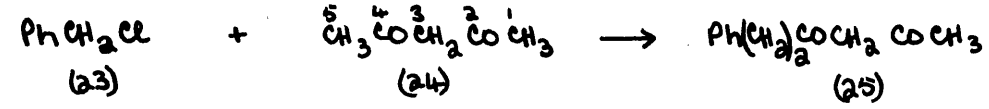
With the structure of the Dieckmann ester firmly established it is of interest to consider briefly its properties and mode of formation. The high $\lambda_{max.}$ in ethanol (310 mμ) comparable with that of the enolate ion of acetylcyclopentanone (307 mμ) suggests that the Dieckmann ester is fully ionised. This is supported by the fact that alkali has little effect on the spectrum while acid causes a displacement of $\lambda_{max.}$ to 278 mμ.

In view of the recent papers published by Hauser et al.[12] it is not so surprising that the intramolecular Claisen condensation (using 4 mols. of base) of the β-keto-ester (13) takes place at C_4 rather than at C_2.



(13) (17)

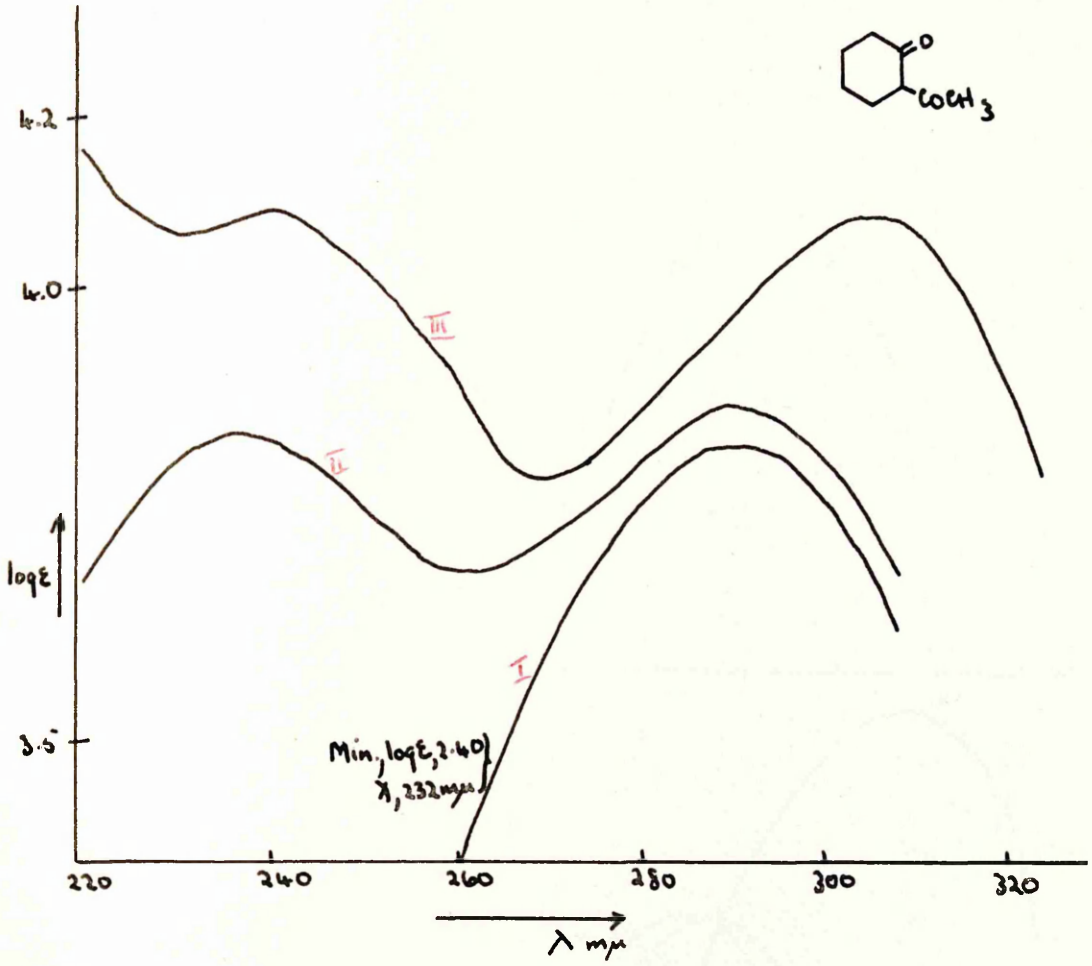
Hauser has shown that benzyl chloride (23) condenses with, for instance, acetylacetone (24) in the presence of 2 mols. of base to give the β-diketone (25), condensation having taken place, not at the activated methylene group (i.e. at C_3), but at the terminal carbon atom (i.e. at C_1 or C_5).



(23) (24) (25)

Attempts to effect intramolecular condensation of the β-keto-ester (13) at the alternative position (C_2), by using only one mol. of base under a variety of conditions, gave, either starting material or a complex mixture.

Fig 1.



I Ethanol, II Ethanol - dil. HCl, III Ethanol - dil NaOH solution.

Fig 3.

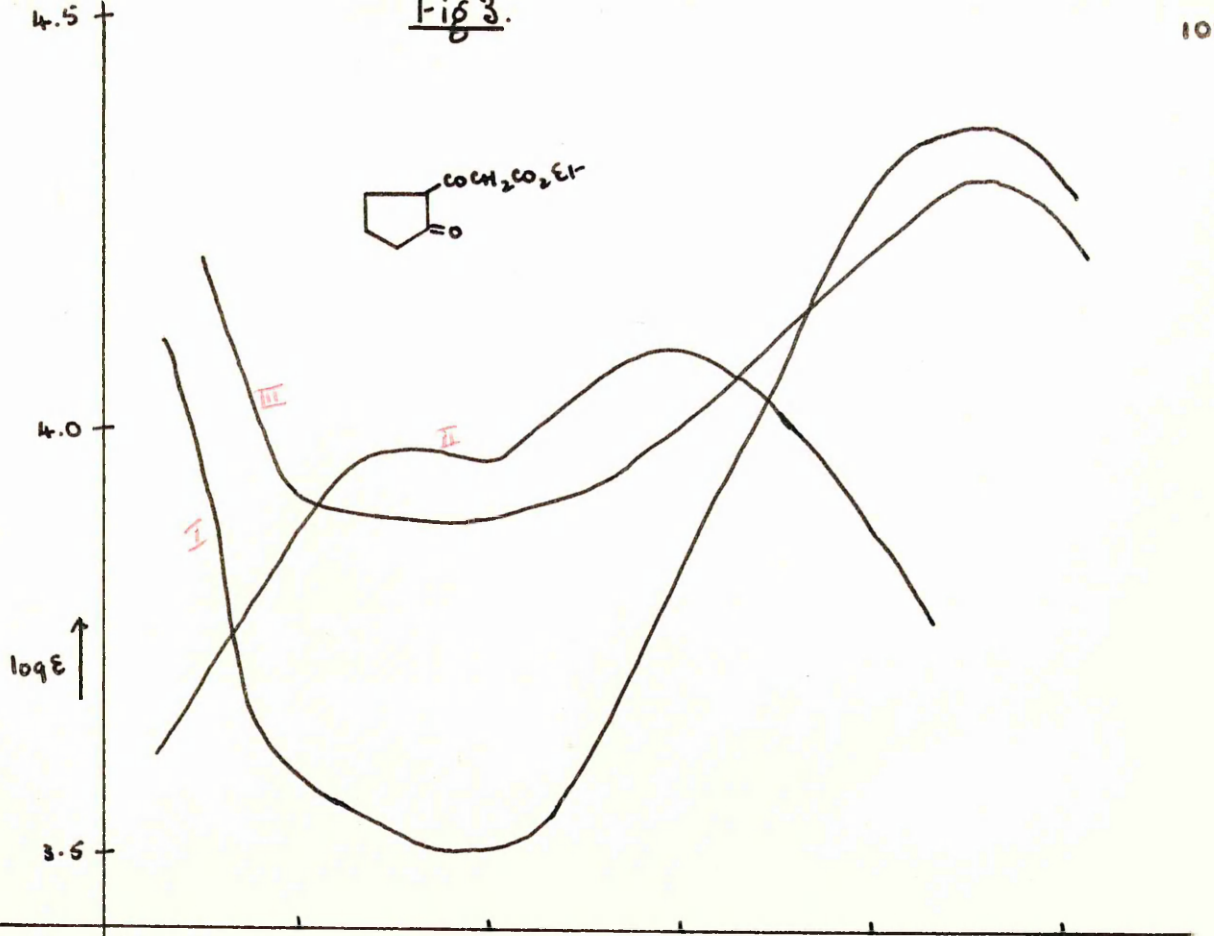
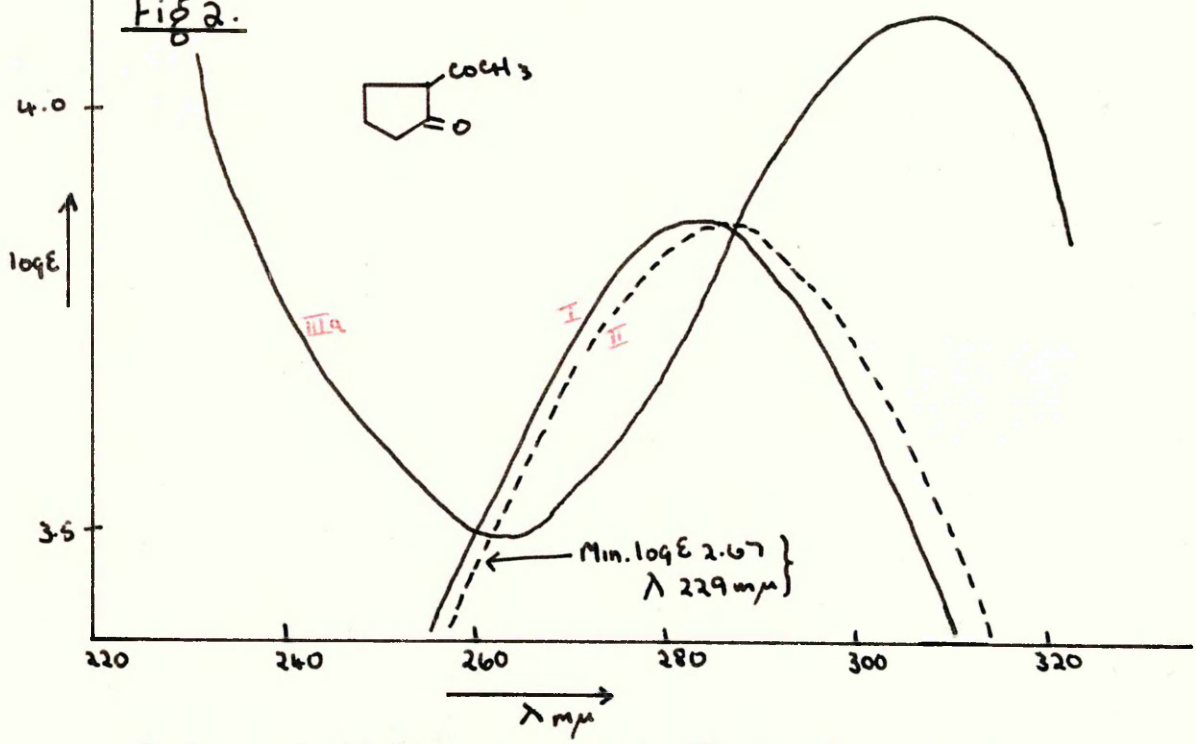


Fig 2.



I Ethanol, II Ethanol - dil. HCl, III Ethanol - dil. NaOH,

IIIa N. NaOH solution.

Fig 6

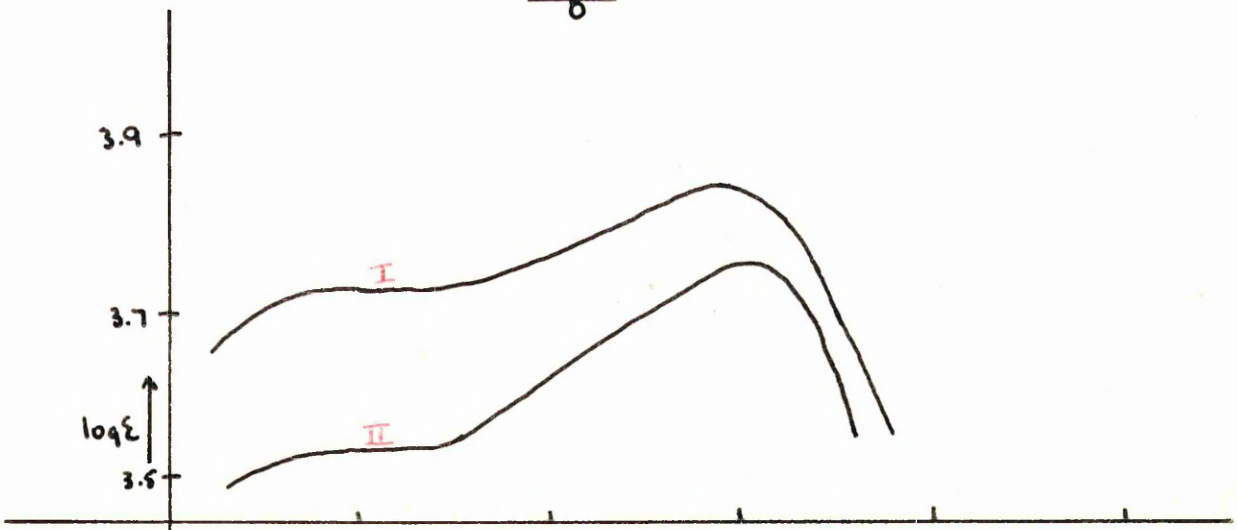
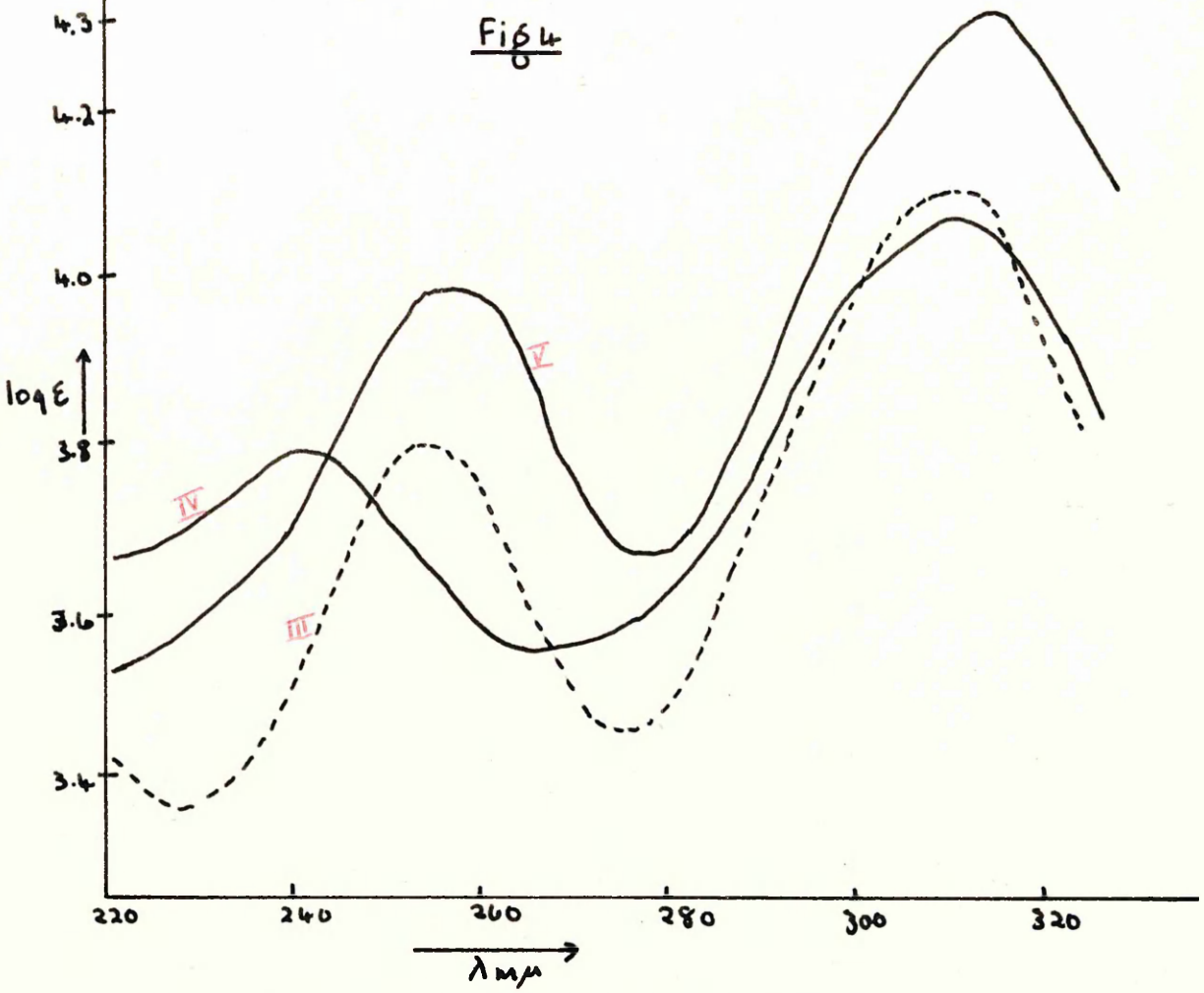


Fig 4



Copper enolates of :- I Acetoacetic ester II $EtO_2C\,CH_2CO(CH_2)_4\,CO_2Et$ (13)

III Acetylcyclopentanone IV Acetylcycloheranone V Dieckmann ester(17).

Fig 5

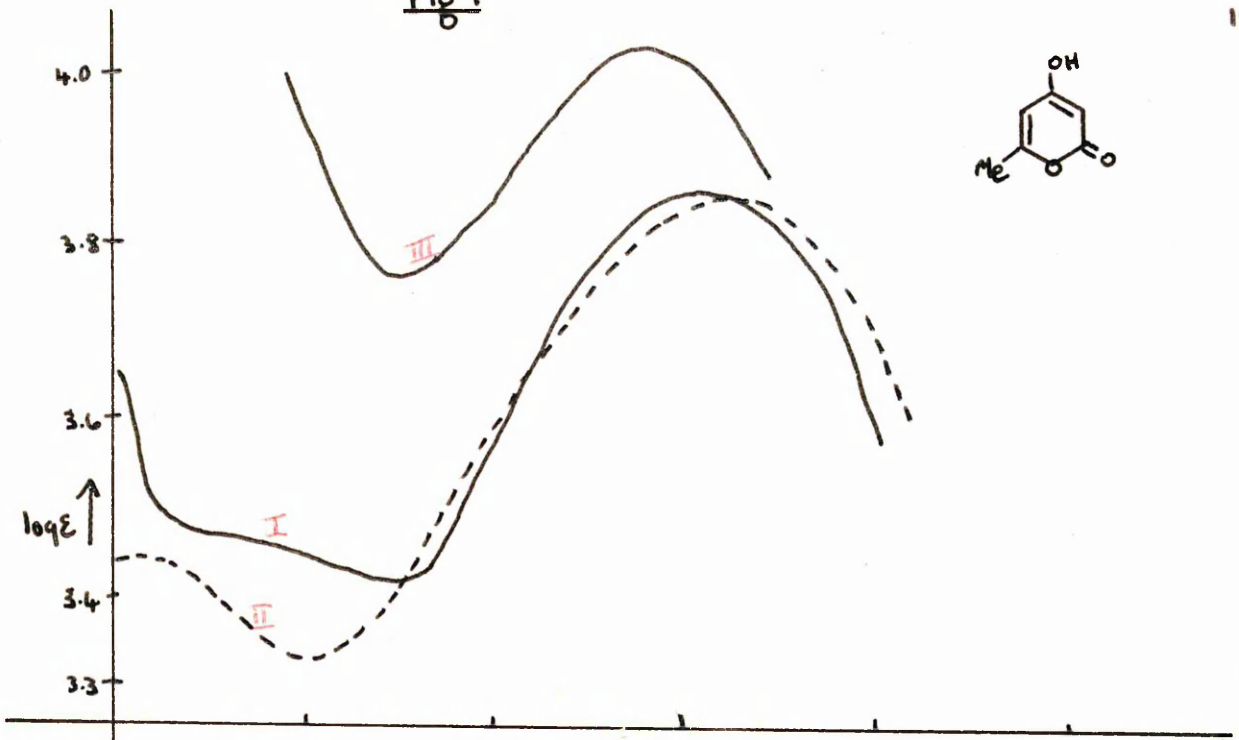
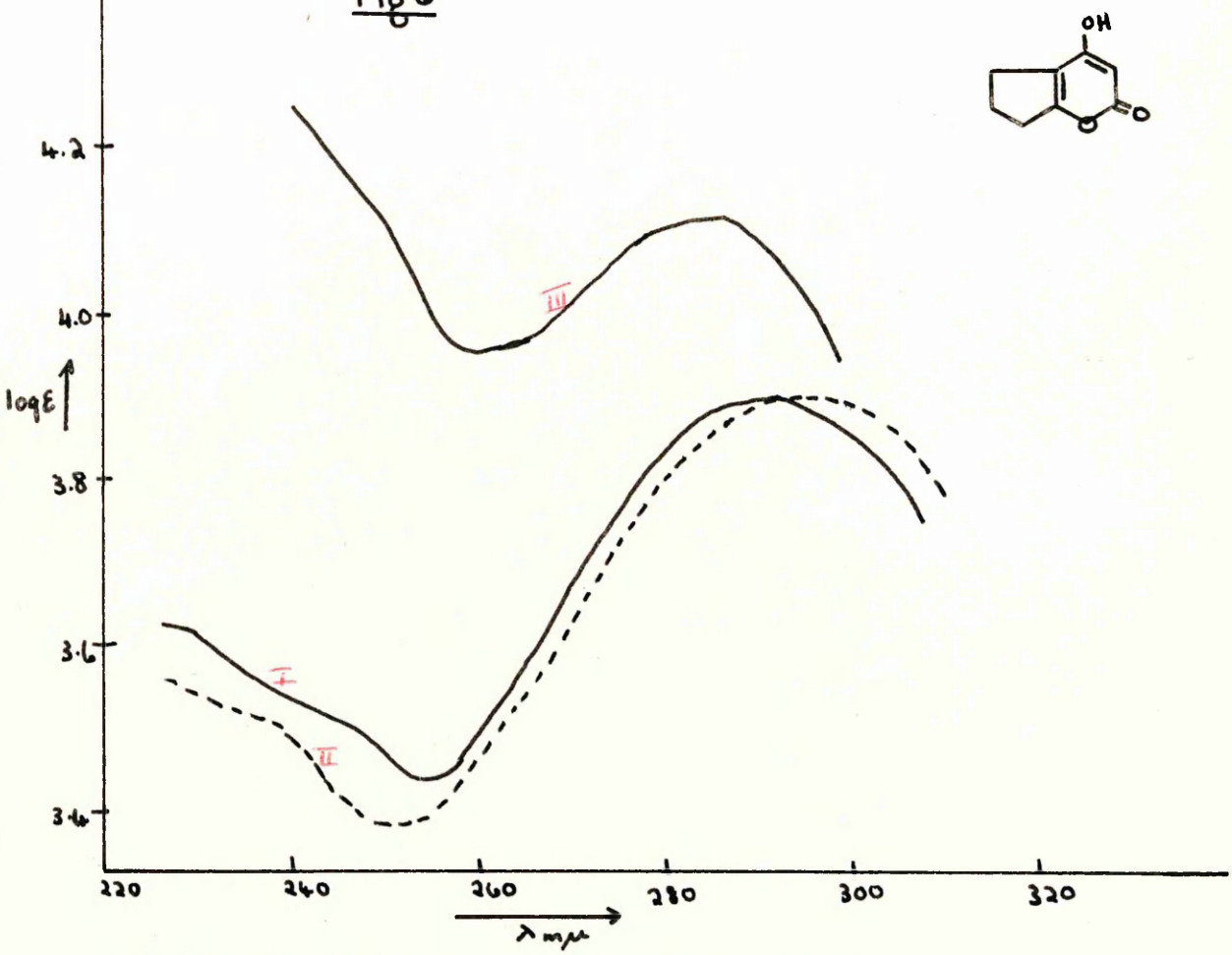


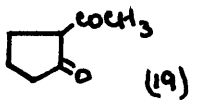
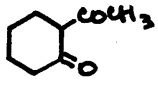
Fig 6



I Ethanol, II Ethanol - dil. HCl, III N. NaOH solution.

Table 1

The ultra-violet spectra of β-dicarbonyl compounds and their copper enolates.*

Compound	Solvent	$\lambda_{max.}$ mμ	$\varepsilon_{max.}$
 (19)	Ethanol	286	7,211
	Ethanol-dil. HCl	284	7,386
	N. NaOH	307	26,360
Copper enolate	Ethanol	254	6,389
		309	12,630
	Ethanol	289	6,998
	Ethanol-	289	7,563
	dil. HCl	236	6,902
	Ethanol-	240	12,380
	dil. NaOH	304	12,090
Copper enolate	Ethanol	240	6,167
		309	12,150
Aceto-acetic ester copper enolate (16)	Ethanol	240 (inflection)	5,142
		278	6,979

* Determined with a Unicam spectrometer.

Table 1 (contd.)

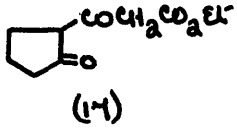
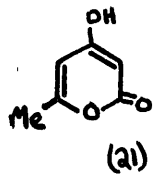
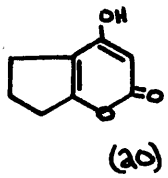
Compound	Solvent	$\lambda_{max.}$ mμ	$\varepsilon_{max.}$
$EtO_2C(CH_2)_4CO$ $EtO_2C\,CH_2$ [(13), n=4]	Ethanol	245	1,789
	Ethanol-dil. HCl	244	2,359
	Ethanol-dil. NaOH	274	30,090
Copper enolate	Ethanol	240 (inflection)	3,386
		279	5,741
 (14)	Ethanol	310	18,210
	Ethanol-dil HCl	253	9,419
		278	12,480
	Ethanol-dil NaOH	311	23,330
Copper enolate	Ethanol	255	9,477
		313	20,040

Table 1 (contd.)

Compound	Solvent	$\lambda_{max.}$ mμ.	$\varepsilon_{max.}$
 (21)	Ethanol	282	7,256
	Ethanol-dil. HCl	284	7,256
	N. NaOH	276	10,610
 (20)	Ethanol	292	8,030
	Ethanol-dil. HCl	295	8,160
	N. NaOH	284.5	13,340

EXPERIMENTAL

Ethyl Hydrogen Adipate [(10)], n = 4]. Ethyl hydrogen adipate was prepared from adipic acid (116 g.) and diethyladipate (94 g.) according to the method of Brown et al.[13]. Distillation of the crude product gave pure ethyl hydrogen adipate (79.5 g.), b.p. 140-142°/2 mm., m.p. 27-30°.

Ethyl Chloro Adipate [(11), n = 4]. Ethyl hydrogen adipate (20.8 g.) and thionyl chloride (12 c.c.) were warmed (3 hrs.) on a water bath at 50-70°. Excess thionyl chloride was removed in vacuo and the product distilled to give the pure acid chloride (21.04 g.), b.p. 90-92°/0.8 mm., n_D^{21} 1.4438.

Ethyl Hydrogen Malonate. Ethyl hydrogen malonate was prepared from diethyl malonate (102 g.) via the mono-potassium salt, according to the method of Strube[14]. The liquid residue was dried at 50°/1 mm. for 1 hour to give pure ethyl hydrogen malonate (55 g.).

Ethyl tert-Butyl Malonate. A 500 c.c., heavy-walled, narrow mouthed bottle was fitted with a thick rubber tube closed by a screw clip. The bottle was connected via a two-way adaptor to a vacuum line (high pressure water) and a dropping funnel. The system, connected to an isobutene

source was evacuated and sealed off with a screw clip. A manometer registered the pressure in the enclosed system. The 500 c.c. bottle was cooled in acetone-carbon dioxide and isobutene passed into the system, the pressure being observed on the manometer. After about 60 c.c. of isobutene had collected in the bottle the flow was stopped and ethyl hydrogen malonate (55 g.) followed by ether (100 c.c.) and concentrated sulphuric acid (3.5 c.c.) added through the dropping funnel. The bottle was closed by means of the screw clip, removed from the cooling mixture and shaken overnight at room temperature. The working up procedure was the same as that described by Strube[14]. Isolation of the ester and distillation gave pure ethyl tert-butyl malonate (41 g.), b.p. 89-90°/13 mm., $n_D^{19.5}$ 1.4160. (lit.,[14] b.p. 98-100°/22 mm., n_D^{23} 1.4142).

Condensation of Ethyl Chloro Adipate with Ethyl tert-Butyl Malonate[15]. Magnesium ethoxide was prepared from magnesium (5.18 g.), dry absolute ethanol (50 c.c.) and dry xylene (10 c.c.) according to the method of Meerwein[16], using a little carbon tetrachloride to initiate the reaction. The solvent was removed and the magnesium ethoxide finally dried in vacuo. Dry ether (180 c.c.) was immediately added followed by ethyl tert-butyl malonate with stirring. The mixture was stirred and heated (½ hr.) under reflux

by which time all the magnesium ethoxide had dissolved. The acid chloride (40.9 g.) in dry ether (50 c.c.) was then added slowly with stirring. Heating under reflux was maintained for 2 hours after which the solution was chilled, treated with water (75 c.c.) and acidified with dilute sulphuric acid (50 c.c. required). The aqueous phase was separated and washed several times with ether. The ether phase and ether washings were dried ($MgSO_4$) and the solvent removed yielding the triester [(12), n = 4] (69 g.), which gave a dark red colour with methanolic ferric chloride.

1:6-Diethoxycarbonylhexan-2-one [(13), n = 4][15]. A solution of the crude triester (69 g.), isolated above, in dry benzene (100 c.c.) was heated under reflux, the returning condensate passing through silica gel. After the last traces of water were thus removed, p-toluene-sulphonic acid (1 g.) was added and heating under reflux continued until isobutene (test: acidified potassium permanganate) and carbon dioxide (test: lime water) ceased to be evolved (2½ hrs.). The solution was cooled, washed with saturated sodium bicarbonate solution (100 c.c.), water, and the benzene phase separated, dried ($MgSO_4$) and the benzene removed. The product was heated in vacuo and

distilled through a fractionating column until the temperature of the vapour had reached 135°/0.6 mm. The fractionating column was removed and the remaining oil distilled to give pure 1:6-diethoxycarbonylhexan-2-one (26.4 g.), b.p. 142-143°/0.8 mm., n_D^{20} 1.4474 (Found: C, 59.29; H, 8.60. $C_{10}H_{20}O_5$ requires C, 59.00; H, 8.25%). The β-keto-ester gave a copper salt melting at room temperature and a dark red colour with methanolic ferric chloride. On heating the β-keto-ester (250 mgs.) with phenylhydrazine (110 mgs.) for 2 hours on the steam bath, the pyrazolone (290 mgs.) was formed, this crystallized from ethyl acetate-light petroleum (b.p. 40-60°) as plates, m.p. 82-84° (Found: C, 66.67; H, 6.69. $C_{16}H_{20}O_3N_2$ requires C, 66.63; H, 6.99%).

Dieckmann Cyclisation of 1:6-Diethoxycarbonylhexan-2-one[6].

A high dilution apparatus was set up in which the returning condensate and solution of β-keto-ester passed through a dilution chamber before entering the reaction vessel. The apparatus was swept out with dry nitrogen, xylene (250 c.c.) added, and heating under reflux maintained for a few minutes until the last traces of moisture had been removed. Potassium (7.7 g.) was added with vigorous mixing (using a vibromischer) followed by tert-butanol

(46.2 c.c.) in xylene (50 c.c.). After heating under reflux for 1 hour (to ensure formation of the potassium tert-butoxide) the xylene/tert-butanol mixture was distilled off until the refractive index of the xylene (n_D^{18} 1.4963) was constant (about 1.5 hrs. required). Heating under reflux and mixing were continued while a solution of the β-keto-ester (10 g.) in xylene (100 c.c.) was added slowly (7½ hrs.) in a nitrogen atmosphere via the dilution chamber. The solution was then heated under reflux for a further ½ hour, cooled, neutralised with glacial acetic acid (19.5 c.c.), washed with three, 50 c.c. portions of water, and the solvent removed in vacuo (bath temperature 40-60°). Distillation of the product yielded 2-(carboethoxyacetyl)-cyclopentanone (17) (5.7 g.), b.p. 120-123°/0.5 mm., n_D^{21} 1.4850 (Found: C, 60.59; H, 7.12. $C_{10}H_{14}O_4$ requires C, 60.32; H, 6.97%), $\nu_{max.}$ (thin film) 1735 (s, -COOEt), 1710 (s, C=O, open chain), 1665 (m, C=O conjugated), 1615 $cm.^{-1}$ (m, C=C conjugated). The 2:4-dinitrophenylhydrazine of the latter after several recrystallizations from ethanol, was obtained as yellow needles, m.p. 189-190° (decomposition) (Found: C, 47.24; H, 3.27; N, 19.77. $C_{22}H_{22}O_{10}N_8$ requires C, 47.30; H, 3.97; N, 20.07%).

The residue from the above distillation, on addition

of a small amount of acetone crystallized as a yellow solid (0.55 g.), m.p. 189-190° (decomposition) and was recrystallized from water as pale yellow needles, m.p. 193-194° (decomposition) (Found: C, 63.28; H, 5.34. $C_8H_8O_3$ requires C, 63.15; H, 5.30%).

While the Dieckmann ester gave a dark red methanolic ferric chloride colour the crystalline substance gave none.

Copper Enolate of Dieckmann Ester. The ester (1.1 g.) in ether (20 c.c.) was added to a solution of copper acetate (2 g.) in water (40 c.c.) and the mixture shaken for 1 hour. The dried, grey, crude copper salt (1.1 g.) was recrystallized from benzene as needles m.p. 179-180° (decomposition). The copper salt, which appeared to decompose on standing in air, yielded the pure ester on shaking ($\frac{1}{2}$ hr.) with dilute hydrochloric acid (2.5 N) and ether.

2-(Carbobenzyloxyacetyl)-cyclopentanone (18). Benzyl alcohol (0.6 g.) was added to the Dieckmann ester (1 g.) in xylene (10 c.c.). The latter was distilled off slowly in a stream of nitrogen during 2 hours more xylene being added dropwise during this time to keep the volume constant. The solvent was removed leaving the crude benzyl ester, $\nu_{max.}$ (thin film) 3490 (w, OH), 1745 (s), 1710 (s), 1660 (s), 1625 (s), 830 (m), 755 (s), 703 cm.$^{-1}$ (s).

Hydrogenalysis of 2-(Carbobenzyloxyacetyl)-cyclopentanone. The ester (0.37 g.) when hydrogenated in ethanol (5 c.c.) over palladised charcoal (0.2 g. of 10%) absorbed hydrogen (43 c.c.; 1.26 mols.) rapidly. The solvent was removed on the water bath in vacuo and the product [0.12 g.; $\lambda_{max.}$ 284 mμ ($\varepsilon_{max.}$ 2,300)] distilled. The infrared spectrum of the distilled oil showed the same peaks as acetylcyclopentanone (prepared below).

4-Hydroxy-5:6-trimethylene-2-pyrone (20). 2-(Carbobenzyloxyacetyl)-cyclopentanone prepared from the Dieckmann ester (1 g.) as above, was heated in vacuo at 150-170° until no more benzyl alcohol distilled (½ hr.). The product, which gave no ferric chloride colouration, was crystallized from acetone-light petroleum (b.p. 40-60°) as cubes (0.33 g.) m.p. 188-193° (decomposition). The pure pyrone obtained as needles (m.p. and mixed m.p. 193-194°) from water had an infrared spectrum, $\nu_{max.}$ (KCl disc) 1675 (s), 1620 (m), 1565 (s), 1494 (s), 906 (w), 878 (m), 817 cm.$^{-1}$ (m), identical with that of the compound $C_8H_8O_3$ obtained as a by-product in the Dieckmann cyclisation (page 113) and also with that of 4-hydroxy-5:6-trimethylene-2-pyrone prepared by Ziegler[11].

Hydrolysis of 4-Hydroxy-5:6-trimethylene-2-pyrone. Dilute sulphuric acid (10 c.c. of 0.25 N) was added to the pyrone (0.2 g.) and the product steam distilled during 1 hour. A solution of copper acetate (0.3 g.) in water (4 c.c.) was added to the distillate. The dried copper salt (0.07 g.) was recrystallized from ethanol-acetone as grey-green needles which decomposed without melting at 220-240° and had an infrared spectrum (nujol mull) identical with that of acetylcyclopentanone copper enolate (prepared below). The above copper enolate was decomposed with dilute hydrochloric acid (2.5 N) in the usual way to give a product whose infrared spectrum was identical with that of acetylcyclopentanone (prepared below).

1-Morpholinocyclopentene. 1-Morpholinocyclopentene was prepared from morpholine (12.12 g.; distilled, b.p. 126-130°) and cyclopentanone (11.70 g.; distilled, b.p. 128-130°) according to the method of Hunig et al.[17]. Unchanged cyclopentanone was removed by distillation through a fractionating column and the product distilled to give pure 1-morpholinocyclopentene (8.5 g.), b.p. 110-112°/7 mm., n_D^{18} 1.5131.

2-Acetylcyclopentanone. 2-Acetylcyclopentanone was prepared from 1-morpholinocyclopentene (5 g.), triethylamine

(3.96 g.; distilled over sodium) and acetyl chloride (2.80 g.) according to the method mentioned above[17]. The crude product was distilled to give acetylcyclopentanone (2.07 g.) which was further purified via the copper enolate. The latter decomposed without melting at 220-240° and was crystallized as needles from ethanol-acetone. Hydrolysis of the copper enolate and distillation of the resulting oil gave pure acetylcyclopentanone (dark red methanolic ferric chloride colour), b.p. 88-90°/17 mm., n_D^{16} 1.4889, $\nu_{max.}$ (thin film) 1740 (m, C=O in five-membered ring), 1704 (s, C=O of acetyl group), 1660 (s, C=O conjugated), 1610 $cm.^{-1}$ (s, C=C conjugated).

Triacetic lactone (21). Triacetic lactone was prepared by the action of sulphuric acid (15 g. of 90%) on dehydroacetic acid (5 g.) according to the method of Collie[9]. The crude, dry, triacetic lactone (2.9 g.) was recrystallized from water as needles, m.p. 175-181° (decomposition). On heating the crystals at 100°/0.5 mm. unchanged dehydroacetic acid (m.p. and mixed m.p. 110-113°) sublimed out. The remaining material on crystallization from water yielded pure triacetic lactone as needles m.p. 190-192° (lit., m.p. 188-189°) (C-methyl estimated by Kuhn-Roth method, 11.28%. Calculated for one $C-CH_3$ grouping, 11.91%), $\nu_{max.}$ (nujol mull) 1707 (s), 1660 (s), 1620 (s),

1585 (s), 1543 (m), 1510 (m), 1494 (m), 991 (s), 878 (m), 841 (s), 814 $cm.^{-1}$ (m). Contrary to previous findings (cf.[8]) triacetic lactone gave no colour with methanolic ferric chloride.

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